Preoperative laboratory tests as predictors of complicated appendicitis

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Background and aims
Diagnosis of acute appendicitis is not always straightforward; even the most experienced surgeon may remove normal appendix or sit on the perforated one. The aim of this study is to investigate the role of preoperative laboratory tests in the prediction of complicated appendicitis (CA).
Patients and methods
A total of 126 patients presented with right iliac fossa pain (appendicitis) were included between March 2018 and January 2019 in the Department of General Surgery, Zagazig University Hospitals. All patients underwent blood sample test, surgical exploration, and management according to operative findings.
Results
According to the operative and histopathological findings, the participants were divided into group A which included 72 (57%) patients with non-CA and group B which included 54 (43%) patients with CA. The preoperative laboratory predictors such as white blood cells (WBCs), international normalized ratio (INR), serum C-reactive protein (CRP), and total bilirubin (TB) were highly significantly higher in group B ($P<0.0001$) than in group A. Serum WBCs and CRP showed the highest sensitivity for defining cases with CA followed by INR and TB (92.6, 92.6, 83.4, 68.75%), respectively, while serum TB showed the highest specificity for defining cases with CA followed by INR, CRP, and WBCs (89.7, 74.5, 67.8, 67.8%), respectively.
Conclusion
The diagnostic accuracy of WBCs, INR, TB, and CRP were between 68% and up to 93% indicating that these preoperative laboratory tests were valid for early detection of CA. Further studies evaluating these laboratory predictors are recommended.

Keywords:
appendicitis, bilirubin, C-reactive protein, international normalized ratio, white blood cells

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Introduction

Acute appendicitis (AA) is the most common surgical abdominal emergency [1]. Diagnosis of AA is not always straightforward. Sometimes, clinical presentation may be atypical, even the most experienced surgeon may deal with normal appendix or sit on the complicated one [2].

It has been demonstrated that a diagnostic approach based solely on history and clinical evaluation caused an unacceptably high percentage of negative appendectomy of between 9.2 and 35% [3,4].

Therefore, a combination of history, examination, laboratory tests, and radiological investigations are preferable for the diagnosis. Most of the physicians apply observation and reevaluation for cases with less typical symptoms and signs. However, this approach may sometimes result in prolonged hospital stay and delayed definitive treatment causing perforation [4].

Occlusion of the lumen of the appendix, in AA, leads to obstruction, distention, impairment of blood flow, and mucosal disruption. Thereafter, bacterial proliferation and leukocytic infiltration develop on this defective area. Migration of leukocytes to the target tissues results in a release of cytokines such as C-reactive protein (CRP). Many studies have reported that an increase in white blood cells (WBCs) has been the earliest sign of appendiceal inflammation, while increased CRP has been noted in more advanced stages of appendicitis [5].

Also, the results have been concluded from using inflammatory markers alongside total bilirubin (TB) in suspected appendicitis cases, often influencing the diagnosis [6].

Although several studies about the prediction of complicated appendicitis (CA) were published, no definite method was able to distinguish between CA and non-CA preoperatively [6–10].

Consequently, the current study aimed to investigate the role of preoperative laboratory tests in the prediction of CA.

Patients and methods

Study design

Between March 2018 and January 2019, a prospective interventional study was carried out in the Department of General Surgery, Zagazig University Hospitals, Egypt. In all, 126 patients were included in our study. The study was approved by the Institutional Review Board and ethics committee of Zagazig University Hospitals. The included patients in the study were AA, recurrent right iliac fossa (RIF) pain or with appendicular masses, managed conservatively and later planned for interval appendicectomy. The patients are with the following criteria, chronic infectious diseases like ileocecal tuberculosis, carcinoid tumors, and other neoplastic lesions of the appendix, pregnancy, advanced liver disease, or biliary disorder, history of multiple abdominal operations, abdominal surgery, or concurrent bowel resection were excluded from the study.

Clinical evaluation was done for all patients. Routine preoperative investigations such as complete blood count, CRP, coagulation profile, liver and kidney function tests, and random blood sugar were done. All patients have had pelviabdominal ultrasonography to detect pelvic-free fluid and appendicular mass, exclude ovarian cyst, and assess the liver state. Informed consent was taken from our patients before the study.

Study method

Patients' history and examination were used whether to admit or discharge the patients suspicious for AA.

All patients gave blood samples during the first hours of admission to the emergency department, which had been sent to the hospital laboratory by a registered nurse for serum CRP, TB, total leukocytic count (TLC), and percentage of polymorphonuclear leukocytes.

All laboratory investigations were conducted at the hospital laboratory [upper limits for normal WBCs, CRP, TB, and international normalized ratio (INR) were 10×109/l, 0.3 mg/dl, 1.2 mg/dl, and 1.22, respectively. A body temperature $>$ 37.2°C was regarded as fever) [11].

Thereafter, all patients underwent surgery and management according to operative findings. The performed surgical methods depended on the ability and the decision of the surgeon, either laparoscopic or open appendectomy. Drainage tubes were inserted for cases with risks for hemorrhage or leakage and in appendicitis with perforation, abscess, or gangrenous change.

Excised specimens were sent in a sterile container with formalin as preservative and examined histopathologically for confirmation of removed appendix status and defining the extent of inflammation.

Histopathologically, catarrhal appendicitis is defined as apparent enlargement of lymphoid follicles in appendiceal mucosa; cellulitis appendicitis is defined as neutrophil infiltration into all layers; gangrenous appendicitis is defined as neutrophil infiltration and muscle layer necrosis; and perforated appendicitis is defined as necrosis and perforation in all layers [12].

On the basis of operative and histopathological findings, cases with catarrhal or cellulitis appendicitis were classified as non-CA (group A), while cases with gangrenous change, perforation, or abscess formation were classified as CA (group B).

Postoperative care and follow-up

Routine postoperative follow-up was performed for all patients including vital signs, abdominal pain or distension, wound infection, and hospital stay.

Results

Operative and histopathological findings

On the basis of these findings, the 126 included patients classified into 72 (57%) patients had non-CA (group A) with 5% catarrhal and 52% cellulitis appendicitis, while the remaining 54 (43%) patients had CA (group B) with 23% gangrenous, 17% perforated appendicitis, and 3% mass.

Demographic characteristics

More than half of group A and group B were men (51.39 and 57%) and more than 30 years old (55.56 and 59.26%, respectively), with no statistically significant difference ($P>0.05$) between both groups: ensuring homogeneity of the studied groups.

Symptoms, signs, and ultrasound findings

All patients presented with right lower quadrant pain and RIF tenderness, while nausea, vomiting, dysuria, bowel disturbances (diarrhea), rebound tenderness, and fever more than 38°C were more in group B (94.4, 59.26, 53.7, 37, 98.15, 90.7%, respectively) than in group A (62.5, 25, 12.5, 5, 72.22, 11%, respectively) with highly statistically significant difference ($P<0.001$) between both groups. The normal ultrasound findings among groups A and B were (27.8 and 14.81%, respectively) and the presence of a rim of free fluid around the appendix was the most preoperative ultrasound findings (68.05%) in group A, while in group B appendicular abscesses (44.44%) were the most preoperative ultrasound findings with highly statistically significant difference ($P<0.001$) (Table 1).

Preoperative laboratory predictors and postoperative outcomes

Preoperative laboratory predictors WBC, INR, CRP, and TB have increased more in group B (96.3, 92.6, 96.3, 88.89%, respectively) than in group A (30.56, 34.7, 41.67, 45.83%, respectively) with highly statistically significant difference ($P<0.001$) between both groups regarding all predictors. Also, the mean hospital stay was highly significantly longer ($P<0.001$) in group B (2.82±0.24 days) than in group A (1.15±0.23 days) and the wound complication (infection) was more in group B (11.11%) than in group A (1.39%) with statistically significant difference between both groups ($P<0.05$) (Table 2).

Diagnostic accuracy of preoperative laboratory predictors

Serum WBCs showed the highest sensitivity and specificity for excluding cases with AA followed by INR, CRP, and TB (85.62, 82.5, 71.34, and 68.75%) and (70, 50, 50, and 50%, respectively) at 95% confidence interval (CI) and also serum CRP showed the highest accuracy for excluding AA cases followed by TB, WBCs, and INR (98.4, 95.18, 84.6, and 76.5%, respectively) at 95% CI, while regarding the definition of cases with CA, serum WBCs, and CRP showed the highest sensitivity followed by INR and TB (92.6, 92.6, 83.4, 68.75%, respectively) at 95% CI. Serum TB showed the highest specificity than INR, CRP, and WBCs (89.7, 74.5, 67.8, 67.8%, respectively) at 95% CI, and serum TB showed the highest accuracy followed by CRP, WBCs, and INR (84.8, 78, 78, 76.67%, respectively) at 95% CI (Table 3).

Discussion

Diagnosis of AA is still challenging even after the advent of ultrasonography, computed tomography scan, and diagnostic laparoscopy. It requires a subjective approach for diagnosis even though all advancement in imaging and laboratory technologies with resultant either perforated appendices in case of conservative approach or negative surgeries if a proactive attitude is maintained by the surgeon [13].

Progression of the inflammatory process increases intraluminal pressure causing appendiceal wall

Table 1 Symptoms, signs, ultrasound findings among the studied groups (*N*=126)

	Group A (*N*=72) [*n* (%)]	Group B (*N*=54) [*n* (%)]	*P* value
Symptoms			
Right lower quadrant pain	72 (100)	54 (100)	–
Nausea	45 (62.5)	51 (94.44)	<0.001**,a
Vomiting	18 (25)	32 (59.26)	<0.001**,a
Dysuria	9 (12.5)	29 (53.7)	<0.001**,a
Bowel disturbances	5 (7)	20 (37.04)	<0.001**,a
Duration (2–7day) (mean±SD)	2.50±0.71	6.79±1.33	<0.001**,b
Signs			
RIF tenderness	72 (100)	54 (100)	–
Rebound tenderness	52 (72.22)	53 (98.15)	<0.001**,a
Fever			
<38°C	64 (89)	5 (9.3)	<0.001**,a
>38°C	8 (11)	49 (90.7)	
Ultrasound findings			
Rim of free fluid	49(68.05)	20 (37.04)	<0.001**,a
Abscess	2(2.8)	24 (44.44)	
Mass	1 (1.4)	2 (3.7)	
Normal finding	20 (27.8)	8 (14.81)	

RIF, right iliac fossa. [a]χ^2 test. [b]Independent *t* test. **Significant if less than 0.05.

Table 2 Preoperative laboratory predictors, add postoperative outcomes among the studied groups (*N*=126)

	Group A (*N*=72) [*n* (%)]	Group B (*N*=54) [*n* (%)]	*P* value
WBC (4–11) (×10^3/μl)			
Normal	50 (69.44)	2 (3.7)	<0.001**,a
Abnormal	22 (30.56)	52 (96.3)	
INR (0.8–1.2)			
Normal	47 (65.3)	4 (7.4)	<0.001**,a
Abnormal	25 (34.7)	50 (92.6)	
CRP (1–5) (mg/dl)			
Normal	42 (58.33)	2 (3.7)	<0.001**,a
Abnormal	30 (41.67)	52 (96.3)	
TB (upto 1.2) (mg/dl)			
Normal	39 (54.17)	6 (11.11)	<0.001**,a
Abnormal	33 (45.83)	48 (88.89)	
Hospital stay (1–3 day)			
Mean±SD	1.15±0.23	2.82±0.24	<0.001**,b
Wound complication			
Yes	1 (1.39)	6 (11.11)	0.01*,a
No	71 (98.61)	48 (88.89)	

CRP, C-reactive protein; INR, international normalized ratio; TB, total bilirubin; WBC, white blood cell. [a]χ^2 test. [b]Independent *t* test. **Significant if less than 0.05.

Table 3 Validity of preoperative laboratory tests in the prediction of whether appendicitis is complicated or noncomplicated among the studied groups (*N*=126)

Preoperative laboratory tests	Sensitivity (%)	Specificity (%)	PVP (%)[a]	PVN (%)[b]	Accuracy (%)	CI (%)
Exclusion of AA						
WBCs	85.62	70	91.4	50.23	84.6	95
INR	82.5	50	87.04	34.72	76.5	95
CRP	71.43	50	77.78	41.67	98.4	95
TB	68.75	50	45.83	72.22	95.18	95
Defining of CA						
WBCs	92.6	67.8	64.3	92.59	78	95
INR	83.4	74.5	63.7	87.04	76.67	95
CRP	92.6	67.8	64.3	92.59	78	95
TB	68.75	89.7	73.6	85.8	84.8	95

AA, Acute appendicitis; CA, complicated appendicitis; CI, confidence interval; CRP, C-reactive protein; INR, international normalized ratio; TB, total bilirubin; WBC, white blood cell. [a]Predictive value for positive. [b]Predictive value for negative.

necrosis and so these markers have been used for the diagnosis. The most widely used markers are WBC counts and CRP values [14]. CRP is an acute-phase reactant that shows an increase of between 8 and 12 h after the onset of inflammatory processes with a peak of between 24 and 48 h and later than that of WBC [15,16].

Clotting pathway is activated as a result of released inflammatory mediators following exposure to infectious agents such as viruses and bacteria, or inflammatory cytokines such as interleukin-1, interleukin-6, and tissue necrosis factors [17].

Hyperbilirubinemia that occurs with systemic infections has been described by several mechanisms including hemolysis, associated with bacteria, causing increased bilirubin load, and endotoxemia resulting in reduced hepatic uptake and canalicular excretion of bilirubin [18,19]. In addition, bacterial endotoxin inhibits cytokine mediation of bile salt transport mechanisms, leading to cholestasis [20,21].

Laboratory tests chosen to aid in the diagnosis of appendicitis are based on their availability, low costs, minimally invasive nature, and repeatability [22].

The study at hand showed that more than half (57%) of the studied participants had non-CA (group A), classified into six patients with catarrhal appendicitis and 66 patients with cellulitis appendicitis, while the remaining 43% of the included patients had CA (group B) who were divided into 29, 21, and four cases with gangrenous appendicitis, perforated appendicitis, and mass, respectively.

Similarly, the study conducted by Abdella and Sayed [23] had 417 patients with appendicitis and 67.8% of

them had non-CA, while the other 32.2% had CA. Also, these were further supported by the results of Kim *et al.* [11], who showed that 76.9%, from 234 included patients with appendicitis, had non-CA and only 23.1% had CA.

In disagreement with the Imaoka *et al.* [12] study they found that among 116 patients with appendicitis, 45% had non-CA categorized into two patients with catarrhal appendicitis and 50 with cellulitis appendicitis, while 55% of the studied patients had CA.

Concerning sex and age distribution, we found that more than half of group A and group B were men (51.39 and 57%) and were more than 30 years old (55.56 and 59.26%, respectively); with no statistically significanct difference ($P>0.05$) between both groups, ensuring homogeneity of the studied groups.

In consistence with the Moon *et al.* [24] study that included 54.6% men and 45.4% women, and also matched with the findings obtained from Adams and Jaunoo [6] study in which their patients were divided into 54.3% men and 45.7% women.

However, Kim *et al.* [11] and Abdella and Sayed [23] mentioned that more than half of their included patients were women (54.9% and 53.8%, respectively) and the remaining 45.1% and 46.2%, respectively, were male patients.

Regarding patients' age, the current findings were similar to the Moon *et al.* [24] and Kim *et al.* [11] studies who found that the mean patients' age was older among the CA group (47.19±22.94 and 39.5±21.7 years, respectively). This can be explained by the incidence of CA becoming higher as the age increases.

In terms of presenting symptoms, the right lower quadrant pain was seen in all patients while nausea, vomiting, dysuria, and bowel disturbances (diarrhea) were more in group B (94.4, 59.26, 53.7, 37%, respectively) than in group A (62.5, 25, 12.5, 5%, respectively) with highly statistically significant difference ($P<0.001$) between both groups.

Another previous study demonstrated that 33.3, 13.2, and 20.4% from the included patients presented with vomiting, diarrhea, and dysuria, respectively [23].

In addition, the current study showed that the tenderness at RIF presented in all patients, while rebound tenderness and fever more than 38°C were more signing in group B (98.15 and 90.7%) than in group A (72.22 and 11%) with highly statistically significant difference ($P<0.001$).

The above-mentioned results were different from the findings reported by another study in which the rebound tenderness at RIF was found in all patients and 60.9% patients presented with fever (<38.5°C) and only 39.1% of them presented with fever (>38.5°C) [23]. As well as the Kim *et al.* [11] study showed that fever was more common sign in non-CA cases (9.4%) than cases with CA (7.4%).

On the basis of the preoperative laboratory predictors, WBC, INR, CRP, and TB were highly significantly higher ($P<0.001$) in group B (96.3, 92.6, 96.3, and 88.89%) than in group A (30.56, 34.7, 41.67, and 45.83%, respectively).

Another study found that the preoperative laboratory markers WBC, CRP, and TB were increased more in CA patients (72.2, 92.6, 68.5%, respectively) than in patients who had non-CA (27.8, 71.1, 23.3%, respectively) with *P* values 0.136, less than 0.001, 0.227, respectively, while INR increased more in non-CA (28%) than in CA cases (14.8%) with a *P* value of less than 0.001 [11].

The study at hand also showed that the mean hospital stay was highly significantly longer ($P<0.001$) in group B (2.82±0.24 days) than in group A (1.15±0.23 days) and in addition wound complication (infection) was significantly higher ($P<0.05$) in group B (11.11%) than in group A (1.39%).

These results were in close agreement with a previous study that found that the hospital stay was longer in patients with elevated CRP and INR; however, the wound complication (infection) was more common in patients who had only elevated INR [11].

As regards the validity of preoperative laboratory predictors in exclusion of cases with AA, serum WBCs showed the highest sensitivity and specificity followed by INR, CRP, and TB (85.62, 82.5, 71.34, and 68.75% and 70, 50, 50, and 50%, respectively) at 95% CI as well as the serum CRP showed the highest accuracy followed by TB, WBCs, and INR (98.4, 95.18, 84.6, and 76.5%, respectively) at 95% CI.

The study carried out by D'Souza *et al.* [25] reported that hyperbilirubinemia was significantly associated with appendicitis versus RIF pain of other etiologies and with perforated appendicitis versus simple

appendicitis 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.

On the other hand, Abdella and Sayed [23] demonstrated that both TLC and CRP markers had high sensitivity (88.7 and 83.6%, respectively) for detection of AA among cases with RIF pain though the low specificity of CRP for diagnosis (57.8%) and the specificity of raised TLC was 71.9%. In addition, for differentiation between AA and CA, elevated serum CRP showed higher specificity than of elevated TLC (70.3, 65.8%, respectively), although there is higher sensitivity of elevated TLC compared with elevated CRP (91.8, 80.6%, respectively).

Whereas regarding the validity of preoperative laboratory predictors in the definition of cases with CA, serum WBCs and CRP showed the highest sensitivity followed by INR and TB (92.6, 92.6, 83.4, 68.75%, respectively) at 95% CI, serum TB showed the highest specificity then INR, CRP, and WBCs (89.7, 74.5, 67.8, 67.8%, respectively) at 95% CI, and serum TB showed the highest accuracy followed by CRP, WBCs, and INR (84.8, 78, 78, 76.67%, respectively) at 95% CI.

The obtained results from the Sand *et al.* [26] study showed that the specificity of hyperbilirubinemia for the detection of appendiceal perforation was 86% versus 55 and 35% for TLC and CRP, respectively, whereas the sensitivity was 70% for hyperbilirubinemia and 81 and 96% for TLC and CRP, respectively. They concluded that patients with hyperbilirubinemia and clinical symptoms of appendicitis should be identified as having higher probability for appendiceal perforation compared with those with normal bilirubin levels.

Noh *et al.* [7] found that WBC, CRP, and TB were significantly higher in CA and the most sensitive markers for diagnosing CA were WBC followed by CRP, while TB showed the highest specificity (74.8%).

Also, Burcharth *et al.* [27] reported that serum TB was significantly higher in patients with appendiceal perforation compared with patients without perforation and that elevated serum TB had a sensitivity ranging from 38 to 77% and specificity ranging from 70 to 87% in the prediction of appendiceal perforation. They concluded that elevated serum TB had low sensitivity but higher specificity for detecting the risk of perforation in appendicitis.

In contrast with the study performed by Emmanuel *et al.* [28] in which the mean TB was higher in patients with AA, with more hyperbilirubinemia on admission (30 vs. 12%), and that hyperbilirubinemia showed a specificity of 88% and positive predictive value of 91% for AA and specificity of 70% for perforation or gangrene.

Conclusion

The diagnostic accuracy of WBCs, INR, TB, and CRP were between 68% and up to 93%, indicating that these preoperative laboratory tests were valid for early detection of CA. Further studies evaluating these laboratory predictors in patients undergoing conservative management for appendicitis are recommended.

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Conflicts of interest

There are no conflicts of interest.

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