

New Laboratory Diagnostic Markers in Diagnosis of Complicated Appendix: A Prospective Study

Original Article

Islam A. Amer, Amr Mohamed Amin, Omar AbdelRaheem Sayed Farghaly Al-Tabari

Department of General Surgery, Oncology and Laparoscopic Surgery, Faculty of Medicine, Sohag University, Egypt.

ABSTRACT

Introduction: Acute appendicitis is one of the commonest surgical emergencies globally. Ensuring prompt surgical intervention with an early diagnosis of complex appendicitis might enhance clinical outcomes. Finding a trustworthy, easily measured marker is essential for the diagnosing complicated appendicitis preoperatively.

Aim: To determine whether hyperbilirubinemia, hyponatremia, and elevated CRP play a role in predicting complicated appendicitis.

Patients and Method: Among cases suffering acute appendicitis who attending the Emergency Department at Sohag University Hospital in the period from January, 2024 to December, 2024. One hundred patients admitted for acute appendicitis were included, subjected to operative management, and postoperative confirmation of acute appendicitis by histopathological assessment. Liver function test including total bilirubin, acute phase reactants CRP, Serum electrolytes including sodium. Also, abdominal ultrasound was performed for all participants

Results: Comparing patients with simple appendicitis, those with complex appendicitis had considerably greater blood bilirubin, reduced sodium, and elevated CRP ($P < 0.001$). Hyponatremia exhibited a sensitivity of 92.3%, specificity of 38.4%, and accuracy of 45.5% when compared to other biomarkers that were investigated for the prediction of complex appendicitis. The sensitivity, specificity, and accuracy of hyperbilirubinemia were 92.3%, 38.4%, and 45.5%, respectively. Regarding the sensitivity, specificity, and accuracy of elevated CRP were 100.0%, 13.9%, and 25.3%, respectively.

Conclusion: Hyperbilirubinemia, hyponatremia, and raised CRP levels are important predictors for complicated appendicitis.

Key Words: Complicated appendicitis, hyperbilirubinemia, hyponatremia.

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Corresponding Author: Amr Mohamed Amin, MSc, Department of General Surgery, Oncology and Laparoscopic Surgery, Faculty of Medicine, Sohag University, Egypt, **Tel.:** 01113486740, **E-mail:** dramramin1982@gmail.com

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INTRODUCTION

Acute appendicitis is one of the most frequent causes of abdominal pain and the commonest cause for emergency abdominal operation^[1]. Mostly, the patient's indications and symptoms are combined to get a diagnosis. However, unusual manifestations are not uncommon as 22% to 30% of people who undergo appendectomies for acute appendicitis may not genuinely have the condition. On the other hand, a patient may develop complex appendicitis with increased morbidity and mortality as a result of a diagnostic delay^[2].

Various blood tests [WBCs, CRP], as well as radiological tests (US, CT), have been investigated to reduce the possibility of negative appendectomies^[2].

Numerous scoring systems, for instance the Alvarado score as well as the Modified Alvarado score, have also been developed to diagnose this condition while considering clinical characteristics and laboratory tests^[3].

According to earlier studies, serum bilirubin might help diagnosing acute appendicitis and predict whether a patient would experience an appendicular perforation^[4]. Furthermore, Zosimas *et al.*, recently found that the diagnostic workup should consider the total serum bilirubin upon admission in order to confirm appendicitis rather than rule it out, without focusing on subgroups of the illness that are more or less severe. White blood cell count and CRP can also be utilized in the diagnostic work-up, but their precision is restricted^[5].

A few studies have also shown hyponatremia as a crucial independent risk factor for acute appendicitis^[6]. It is still unclear if hyponatremia is a reliable preoperative diagnostic indicator for complex appendicitis^[7].

This study sought to determine whether elevated CRP, hyponatremia, and hyperbilirubinemia were predictive of appendicular perforation in acute appendicitis in patients

who visited the emergency room of Sohag University Hospital between January 1, 2024, and December 31, 2024.

PATIENTS AND METHODS

Study design:

The Emergency Department of General Surgery, Oncology, and Laparoscopic Surgery department at Sohag University Hospital conducted this hospital-based cohort research between January 1, 2024, and December 31, 2024. The study's target population consisted of all patients who arrived with abdominal discomfort at the General Surgery, Oncology, and Laparoscopic Surgery Emergency Department at Sohag University Hospital, Sohag, and were later diagnosed with acute appendicitis.

Sample size:

The current study employed the total coverage method, which included all cases who presented with abdominal pain to the emergency departments of general surgery, oncology, and laparoscopic surgery at Sohag University Hospital and were diagnosed with acute appendicitis during a one-year period beginning on January 1, 2024, and ending on December 31, 2024.

The 100 patients in the current study were approved to have acute appendicitis; the stage of appendicitis was classified as either early acute, acute suppurative, acute necrotizing gangrenous with perforation, or another kind of appendicitis based on the gross findings after surgery. The main outcome of interest was complicated appendicitis, which is defined as intraoperative observations of acute necrotizing gangrenous appendicitis with perforation.

The following three groups of patients were created using the gross results of the appendix samples: Group 1: Early acute appendicitis was seen in 46 instances (46%) of the group. Group 2: Acute suppurative appendicitis was seen in 41 instances (41%). Group 3: Complicated appendicitis was seen in 13 instances (13%).

Inclusion criteria:

Patients of both sexes, ages 7 to 60, who were hospitalized with acute appendicitis, had surgery, and had postoperative gross confirmation of acute appendicitis. Lastly, the instances that agreed to take part in our research.

Exclusion criteria:

Individuals with known hepatocellular carcinoma, liver illness, liver transplant, chronic use of alcohol, CBD, pregnancy, hemolytic disease, or appendicular tumor.

Patients without a report on histopathology. Patients declined to take part in the present research.

Methodology:

The following first evaluation was performed on eligible patients: Complete history taking, systemic

examination for surgical fitness, including abdominal and cardiothoracic examinations.

Tests in the lab: Five milliliters of venous blood samples were taken for hemoglobin and CBC. Total bilirubin, acute phase reactants (CRP), and serum electrolytes, particularly salt, are all part of the liver function test. Additionally, an abdominal ultrasound was carried out.

Operative procedure:

For open appendectomies, the patient was positioned supine in the operating room with both arms outstretched. From immediately above the bilateral costal borders, a sterile surgical area was established that extended laterally to the right and left sides and inferiorly to the pubic tubercle.

Every patient suspected of having an open appendectomy had a traditional 5cm grid-iron incision on McBurney's spot. After that, a scalpel was used to cut the epidermis and dermis. The external aponeurosis was dissected by electrocautery and blunt dissection. The internal oblique and transverse abdominal muscles were cut open by blunt dissection, revealing the peritoneum, which was then gripped and cut. Finding the appendix was the next priority. After it was located, the mesoappendix was dissected and ligated with Vicryl 2-0. After that, the base of the appendix was squashed and tied up. They removed and excised the appendix.

Hemostasis was confirmed. Good mopping of surgical field, paracolic gutter and pelvis, insertion of intra-peritoneal drain might be needed especially if there is pus collection. Lastly, closure of incision in layers.

Statistical analysis:

Version 22 of SPSS (Statistical Package for the Social Sciences; SPSS Inc., Chicago, IL, USA) was employed to perform all statistical computations. The data were statistically reported using the mean±standard deviation (±SD), or median and range if not normally distributed, as well as relative frequencies (percentages) when applicable and frequencies (number of instances). Since the data weren't normally distributed, the Kruskal-Wallis test was used to compare the quantitative variables. Using the Chi square (χ^2) test, categorical data were compared. When the estimated frequency was less than five, the exact test was utilized instead. To predict complex appendicitis, logistic regression and the odds ratio (OR) with 95% CI were computed. At the 0.05 level, the *P*-value is always two-tailed and significant.

RESULTS

Determine whether hyperbilirubinemia hyponatremia and elevated CRP play a role in predicting appendicular perforation in acute appendicitis (Tables 1-3).

Table 1: Demographic and clinical criteria based on the stages of appendicitis:

Variable name	Total cases, <i>n</i> = 100	Early acute, <i>n</i> = 46 (1)	Acute suppurative, <i>n</i> = 41 (2)	Acute necrotizing gangrenous, <i>n</i> =13 (3)	<i>P</i> value
Age (years)					All: 0.508
Mean±SD	22.33±10.30	22.29±11.98	23.13±9.87	20.00±2.65	1 vs 2: 0.722
Median (range)	20(7–60)	19(7–60)	22(11–54)	20(16–24)	1 vs 3: 0.236
Sex					2 vs 3: 0.075
					All: 0.784
Male	40(40.0%)	19(41.3%)	17(41.5%)	4(30.8%)	1 vs 2: 0.839
Female	60(60.0%)	27(58.7%)	24(58.5%)	9(69.2%)	1 vs 3: 0.491
Serum Sodium					2 vs 3: 0.490
Mean±SD	132.70±5.47	135.24±5.13	131.42±4.30	127.92±5.65	All: <0.001
Median (range)	132(117–145)	135(124–145)	131(119–143)	130(117–137)	1 vs 2: <0.001
					1 vs 3: <0.001
Normal	35(35.0%)	26(56.5%)	8(19.5%)	1(7.7%)	2 vs 3: 0.011
Hyponatremia	65(65.0%)	20(43.5%)	33(80.5%)	12(92.3%)	All: <0.001
					1 vs 2: <0.001
Total bilirubin					1 vs 3: 0.001
Mean±SD	25.44±10.52	20.47±8.91	30.41±10.72	27.00±7.00	2 vs 3: 0.319
Median (range)	26(9–56)	17(9–45)	30(11–56)	25(19–43)	All: <0.001
					1 vs 2: <0.001
Normal	35(35.0%)	27(58.7%)	7(17.1%)	1(7.7%)	1 vs 3: 0.007
Hyperbilirubinemia	65(65.0%)	19(41.3%)	34(82.9%)	12(92.3%)	2 vs 3: 0.189
					All: <0.001
C-reactive protein					1 vs 2: <0.001
Mean±SD	6.76±4.51	4.19±3.13	8.39±4.66	10.54±2.93	1 vs 3: <0.001
Median (range)	7.0(0.3–21.0)	4.0(0.3–14.0)	7.0(0.8–21.0)	10.0(8.0–17.0)	2 vs 3: 0.054
Normal	13(13.0%)	12(26.1%)	1(2.4%)	0(0.0%)	All: 0.003
Raised	87(87.0%)	34(73.9%)	40(97.6%)	13(100.0%)	1 vs 2: 0.002
					1 vs 3: 0.039
Hyperbilirubinemia+hyponatremia	64(64.0%)	19(41.3%)	33(80.5%)	12(92.3%)	2 vs 3: 0.570
					All: <0.001
Hyperbilirubinemia+hyponatremia+ raised CRP	87(87.0%)	34(73.9%)	40(97.6%)	13(100.0%)	1 vs 2: <0.001
					1 vs 3: 0.001
					2 vs 3: 0.319
					All: 0.003
					1 vs 2: 0.002
					1 vs 3: 0.039
					2 vs 3: 0.570

Quantitative data are presented as mean±SD and median (range); Qualitative data are presented as number (percentage); Significance defined by $p<0.05$.

Table 2: The sensitivity and specificity for prediction of complicated appendicitis by used markers ($n= 100$):

Markers	Sensitivity	Specificity	PPV	NPV	Accuracy
Hyponatremia	92.3%	38.4%	18.5%	97.1%	45.5%
Hyperbilirubinemia	92.3%	38.4%	18.5%	97.1%	45.5%
Raised CRP	100.0%	13.9%	14.9%	100.0%	25.3%
Hyponatremia+Hyperbilirubinemia	92.3%	39.5%	18.8%	97.1%	46.5%
Hyponatremia+ Hyperbilirubinemia, raised CRP	100.0%	13.9%	14.9%	100.0%	25.3%

CRP: C-reactive protein; PPV: Positive predictive value; NPV: Negative predictive value.

Table 3: Logistic regression analysis for the risk of complicated appendicitis:

Variables	OR	95% CI	P value
Age	0.971	0.907 – 1.038	0.382
Female sex	1.544	0.441 – 5.411	0.497
Hyponatremia	7.472	0.928 – 60.154	0.059
Hyperbilirubinemia	7.472	0.928 – 60.154	0.059
Hyponatremia+Hyperbilirubinemia	7.846	0.975 – 63.137	0.053

CI: Confidence interval; OR: Odds ratio; *: P value is significant ≤ 0.05 .

DISCUSSION

Hyperbilirubinemia's diagnostic significance in predicting CA has been validated by prior research^[8].

Of the 100 patients who were recruited in the current study and had histologically confirmed appendicitis, 13.1% had complex appendicitis. In contrast to 42.2% of cases with early acute appendicitis and 82.9% of cases with acute suppurative appendicitis, 92.3% of patients with complex appendicitis exhibited hyperbilirubinemia, which refers to a TBIL level of exceeding 20 μ mol/L ($P < 0.001$). The probable contribution of confounding factors to increase bilirubin level were eliminated because this study ruled out cases suffering hepatic problems, liver transplant, chronic alcoholism, congenital biliary disease, pregnancy, detection of appendicular neoplasm, hemolytic diseases, or known HCC. Additionally, serum bilirubin levels were measured prior to surgery. Furthermore, we found that the more severe the appendicitis, the higher the serum bilirubin level, pointing to a possible link between high serum bilirubin level and acute appendicitis severity.

This finding was confirmed by the previous studies that stated that cases with complicated appendicitis had a higher mean serum bilirubin level than that of nonperforated, uncomplicated acute appendicitis cases^[9-11].

The fact that endotoxemia can cause hyperbilirubinemia in situations of simple, perforated, or gangrenous appendicitis may help to explain this discovery^[12]. According to Estrada *et al.*, the pathophysiology of appendicitis determines the high blood bilirubin level^[13]. Notably, mucosal ulceration, a hallmark of early appendicitis, facilitates the passage of bacteria into the muscularis propria of the appendix. Bacterial invasion triggers the human immune system that results in elevated intraluminal pressure, inflammation, and edema. Because of these changes, the appendix develops ischemia necrosis, which promotes direct bacterial infiltration into the circulation and leads to gangrene. As a result, bacterial endotoxins cause bilirubin to be released into the bile ducts, which raises the quantity of bilirubin in the blood^[13].

Furthermore, a study examining the predictive power of serum bilirubin levels for complicated appendicitis prediction found that hyperbilirubinemia had a high negative predictive value (NPV) and a high sensitivity for

complicated appendicitis prediction. Hyperbilirubinemia's overall accuracy in predicting complex appendicitis is impacted by its low specificity and positive predictive value (PPV), which are insufficient for this condition. Therefore, a pre-operative increase in serum bilirubin levels may be used as a highly sensitive biomarker, meaning that fewer cases of complicated appendicitis are missed due to false negative results. This could help prevent the consequences of complicated appendicitis, but it may also increase the number of unnecessary appendectomy cases.

Sand *et al.*, conducted a retrospective analysis with 538 participants to look at serum bilirubin levels. According to the study, the specificity of hyperbilirubinemia in predicting perforated appendicitis was 86%^[14]. The specificity and sensitivity of elevated bilirubin levels in predicting perforated appendicitis were 87.21% and 77.8%, respectively, with a PPV of 45.2% and an NPV of 96.7%, according to a different retrospective research conducted by Atahan *et al.*, (2011)^[15].

According to McGowan *et al.*, (2013), elevated serum bilirubin levels have also been associated with the latter stages of appendicitis, with a sensitivity of 62.96% and a specificity of 88.31%^[16].

Additionally, pre-operative blood bilirubin levels were shown to have a sensitivity of 9.4%, specificity of 93.0%, PPV of 24.0%, and NPV of 82.0% for predicting perforated appendicitis by Adams and Jaunoo^[17].

According to Bakshi and Colleges (2021), the blood bilirubin level had a 91.4% sensitivity, 88.0% specificity, 78.0% PPV, and 95.7% NPV in predicting complex appendicitis^[18].

Because of its low sensitivity and specificity, hyperbilirubinemia may not be an effective indicator of complex appendicitis, according to a retrospective study by Shuaib *et al.*, (2022) that looked at the effectiveness of hyperbilirubinemia, hyponatremia, and both combined in the pre-operative diagnosis of complicated appendicitis^[19]. However, the NPV was 93.6%.

In the current study patient with hyperbilirubinemia had higher probability of developing complicated appendicitis (OR= 7.472; 95% CI=0.928–60.154), with borderline

significance ($P=0.059$), absent significant result in the current study might be due to small sample size with negatively affect the statistical power of the current study. In McGowan *et al.*, (2013) study author revealed that for every one unit increase in bilirubin the probability of complicated appendicitis had an OR of 1.005 (95.0% CI=1.003-1.008, $P<0.001$)^[16].

Additionally, hyperbilirubinemia was a risk factor for gangrenous appendicitis among 410 cases in Japan, according to Nomura *et al.*, (2014) (OR=1.7919; 95% CI=1.056-3.044, $P<0.05$)^[20]. In a research by Eren *et al.*, (2016), multivariate analysis revealed that a 36-fold increased risk of complex appendicitis was linked to elevated blood bilirubin levels^[11]. Additionally, hyperbilirubinemia was shown to have an odds ratio of 1.99 as a risk factor for complex appendicitis in patients under 65 years of age in the Akai *et al.*, (2019) research^[21].

Based on these findings, the current research suggests that elevated TBIL along with other manifestations of complicated appendicitis might be enough to justify an appendectomy since hyperbilirubinemia may be a sensitive biomarker of complex appendicitis.

A further diagnostic method for complex appendicitis is serum sodium^[22]. Recent research has indicated a correlation between lower blood sodium levels and more severe appendicitis, ranging from simple to complex^[23]. This conclusion was also supported by the current investigation, which revealed that the severity of appendicitis significantly influenced the serum sodium levels. In contrast to 44.4% of cases with early acute appendicitis and 80.5% of cases with acute suppurative appendicitis, 92.3% of patients with complex appendicitis experienced hyponatremia, which was defined as a blood Na⁺ level of less than 135.0mEq/L ($P<0.001$).

Pérez-Soto *et al.*, (2021) showed a lower prevalence of hyponatremia, with hyponatremia occurring in 54.8% of complex patients compared to 29.2% of simple patients^[24].

Furthermore, a high sensitivity (92.3%) was found for the prediction of complex appendicitis by hyponatremia, but a low specificity (38.4%) and an accuracy of 45.5% were also observed. However, a study that looked at the predictive power of hyponatremia and hyperbilirubinemia together found that they only slightly improved specificity and overall accuracy (sensitivity of 92.3%, specificity of 39.5%, and accuracy of 46.5%), and did not contribute to the prediction of complex appendicitis. Hyponatremia was proved to have a sensitivity of 84.4% and a specificity of 45.6% in prediction of complex appendicitis, based on a recent study by Shuaib *et al.*, (2022). But contrary to the present discovery, Shuaib *et al.*, (2022) revealed that the diagnostic efficacy of both hyponatremia and hyperbilirubinemia taken together enhance the prediction ability for complicated appendicitis^[25].

According to Pérez-Soto *et al.*, (2021), the predictive efficacy of hyponatremia in predicting complex appendicitis had a specificity of 57% and a sensitivity of 66%^[24].

A variety of disorders, including as dengue, malaria, HIV, encephalitis, meningitis, pneumonia, and TB, have been related to hyponatremia, an electrolyte imbalance that may serve as a proxy for disease severity^[25]. The pathophysiology of hyponatremia may differ among patient populations. One significant similarity between them is that the sickness may be brought on by an early systemic inflammatory response that is mediated via vasopressin and IL-6^[26].

Hyponatremia (≤ 136 mEq/L) was determined to have an odds ratio of 3.1 (95% CI= 2.0-4.9, $P<0.01$) for predicting complex appendicitis by Pham *et al.*, in (2016)^[6]. Additionally, at a plasma Na⁺ threshold of 136mEq/L, Heymowski *et al.*, found an odds ratio of 2.8 (95% CI, 2.3–3.5) for developing complex appendicitis^[27]. This number is, however, far lower than the odds ratio of 31.9 (6.3–161.9) found in a more recent research by Lindestam *et al.*, (2020). Furthermore, the author found that, in comparison to values >136 mmol/L, hyponatremia revealed a sensitivity of 82.0% and a specificity of 87.0% for anticipation of complex appendicitis, or a 15-fold increase in perforation relative risk (RR) (RR= 15, 95% CI, 3.7–62)^[28].

In the current study patient with hyponatremia, had higher probability of developing complicated appendicitis (OR= 7.472; 95% CI=0.928–60.154), with borderline significance ($P=0.059$). In addition, combined hyponatremia and hyperbilirubinemia slightly increase the predictive ability for complicated appendicitis (OR= 7.846; 95% CI=0.975–63.137), but also with borderline significance ($P=0.053$), absent significant result in our study might be due to the small sample size with negatively affect the statistical power of the current study.

According to a number of investigations, laboratory measures like CRP can be employed to predict perforation in appendicitis and related conditions^[15].

100.0% of the cases with complicated appendicitis in the current study had elevated CRP levels, which were defined as higher than 1.0mg/dL. This is in contrast to 75.6% of patients with early acute appendicitis and 97.6% of patients with acute suppurative appendicitis ($P=0.003$). The significance of other laboratory parameters, such as CRP, has also been assessed in the studied cases. Käser *et al.*, (2010) and Nomura *et al.*, (2014) found statistically significant higher CRP among cases with complicated appendicitis (26, 21), and Eren *et al.*, found a correlation between complicated appendicitis and elevated CRP (>0.5 mg/dL) in another study involving 162 patients^[11]. These findings are consistent with the current findings.

Raised CRP exhibited a high sensitivity (100.0%) and low specificity (13.9%), resulting in a low accuracy of 25.3% in predicting complex appendicitis, according to the current study's prediction capacity of CRP. Similarly, Sand *et al.*, (2009) looked at 538 patients to find out how useful CRP was for diagnosing complicated appendicitis. They found that CRP had a high sensitivity and a low specificity for diagnosing complicated appendicitis; the authors reported that CRP's sensitivity and specificity were 96.0% and 35%, respectively^[14].

The indicators of age, hyperbilirubinemia, CRP, leucocyte count, and perforated appendicitis were compared in another retrospective cohort study that was carried out at two sites with 155 instances of perforated appendicitis and 570 cases of non-perforated appendicitis. CRP>5mg/l showed a sensitivity of 98.0%, a specificity of 28.0%, a PPV of 27.0%, and an NPV of 98.0%, despite the fact that they found that CRP is a better indication of perforation than other biomarkers that were tested^[28].

According to multivariate analysis in Eren *et al.*, (2016), high CRP level was accompanied by 14 times greater risk for complicated appendicitis^[11]. In the current study we couldn't include CRP as an independent indicator of complicated appendicitis as all enrolled cases with complicated appendicitis had raised CRP level.

Based on the current findings we could conclude that the pre-operative evaluation of serum bilirubin, serum sodium, and CRP levels should be routinely performed in cases with suspected appendicitis. These biomarkers could be used as important biomarkers of complicated appendicitis. However, due to low specificity of these biomarkers, their elevation is more likely to produce a high number of false positives and may incorrectly identify cases with complicated appendicitis when it is not actually present which means elevated levels of unnecessary appendectomy. Thus, we didn't recommend using these biomarkers alone for diagnosing complicated appendicitis but must be associated with other clinically suspected manifestations.

LIMITATIONS

The main limitation is that it is a single center study; hence, the results couldn't be generalized to other settings in Egypt or other countries. Secondly, the relatively small number of study participants. This might have reduced the power of the study to detect the prognostic role of the studied biomarkers in predicting complicated appendicitis.

CONCLUSION

Hyperbilirubinemia, hyponatremia, and raised CRP levels are important predictors for complicated appendicitis. These parameters may be helpful in early detection of complicated appendicitis, but still clinical

and radiological diagnoses are still helpful in diagnoses of complicated appendicitis

CONFLICT OF INTERESTS

There are no conflicts of interest.

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