





A Case-control Study on the Correlation between Serum Bilirubin Levels and Various Types of Appendicitis

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Abstract:

Background: Acute appendicitis is one of the most common types of surgical emergencies. Among laboratory factors, hyperbilirubinemia has recently been identified as a strong predictor of preoperative perforation and gangrene.

Aim: This study aimed to investigate the correlation between serum bilirubin levels and types of appendicitis.

Methods: This case-control study was conducted in 2022 using the convenience sampling method on 100 patients who were referred to the emergency department of Imam Khomeini Hospital in Jiroft with abdominal pain. These patients were diagnosed with appendicitis based on the initial clinical examinations. The white blood cells and total bilirubin levels were measured for all the patients. Intraoperative macroscopic findings were recorded by the surgeon, and the pathological results of the specimen were reported. Data was analyzed using SPSS 24, including descriptive and inferential statistics at the significance level of $P < 0.05$.

Results: Among 100 patients aged between 28.5 ± 14.8 , 48% were men, and the rest were women. There was a significant difference between the mean of bilirubin levels in patients with complicated and uncomplicated appendicitis ($P < 0.01$). The results of logistic regression analysis showed that the period of onset of symptoms to hospitalization, leukocytosis level, and preoperative total bilirubin level were significant variables for diagnosing complicated appendicitis ($P < 0.05$).

Conclusion: In this study, we found that patients with complicated appendicitis had higher total bilirubin levels than patients with uncomplicated appendicitis. Therefore, patients with hyperbilirubinemia and clinical symptoms of appendicitis should be considered as more probable cases of perforation than those with normal bilirubin levels.

Keywords: Hyperbilirubinemia, Appendicitis, Perforation, Gangrene, Serum, Bilirubin.

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1. INTRODUCTION

Acute appendicitis is one of the most common types of surgical emergency. The lifetime risk of appendectomy is 13% in men and 25% in women, and the most common age for appendicitis is between 20 and 40. Acute appendicitis is diagnosed based on history, clinical examinations, and laboratory findings. Sometimes, a definitive clinical diagnosis of the disease may also be difficult for experienced surgeons [1-4].

Based on the studies, the prevalence of negative appendectomy varies from 15% to 50% in patients. It is noteworthy that incorrect diagnosis of acute appendicitis is more common in women. The reason is the wide differential diagnosis of gynecological issues such as ectopic pregnancy, ovarian torsion, mittelschmerz, etc. Different scoring systems have been designed to help diagnose acute appendicitis, including criteria for inflammatory response and the Alvarado scale [5-7]. However, unlike different methods, it seems that mistakes in diagnosing the disease have not yet diminished. CT scan findings have high specificity but low sensitivity, whereas perforation diagnosis based on these findings is possible in the presence of abscess or air outside the lumen [8, 9].

Laboratory findings such as WBC and CRP are useful for diagnosis [10]. However, both have low specificity. Bilirubin had a higher specificity than both WBC and CRP [11]. Among the various laboratory factors used to diagnose and predict the complications of appendicitis, hyperbilirubinemia has recently been suggested as a strong predictor for the diagnosis of preoperative perforation and gangrene. Its pathophysiology may be due to bacterial infections and inflammatory factors causing disorder in bilirubin clearance, and an increase in its production during perforation, and bacteria such as *Bacteroides fragilis* and *E. coli* have been more involved in these cases [11-13].

Although negative appendectomy occurs frequently and is part of the surgeon's record, some measures may be taken to reduce the incidence of negative appendectomy and cases of missed acute appendicitis because unnecessary surgery imposes significant stress and complications on the patients and their families. This study was performed to determine the relationship between serum bilirubin level and type of appendicitis to find a factor for early diagnosis and correct surgical intervention to reduce morbidity caused by appendicitis complications.

We hope that the results of this study help surgeons make early diagnoses.

2. METHODS AND MATERIALS

This case-control study was conducted in 2022 using the convenience sampling method on 100 patients who were referred to the emergency department of Imam Khomeini Hospital in Jiroft with abdominal pain. These patients were diagnosed with appendicitis based on the initial clinical examinations. According to the Parsa *et al.* study (2012), with the considered sample size formula for a case-control study, power of 80% and 0.05 type I error, the sample size required for the present study was 100 including 50 patients for the case group and 50 patients for the control group. Patients in the control group had uncomplicated appendicitis [8]. Two groups of information were collected through a checklist. The checklist consisted of two parts: demographic features and test results. The white blood cells of each patient were counted routinely, and we also measured total bilirubin levels. A pars test kit was used to measure total bilirubin, and values greater than 1.2 ml/dl were considered hyperbilirubinemia. Intraoperative macroscopic findings and the pathologic result of the sample were recorded for patients undergoing surgery. Complicated cases included perforated and gangrenous appendicitis (no phlegmon was found).

Inclusion criteria were informed consent, and exclusion criteria included patients who were discharged with general improvement before surgery, patients with a history of alcoholism, viral hepatitis, Gilbert and Dubin-Johnson Syndrome, cholestasis and other biliary diseases, hemolytic and liver diseases associated with hyperbilirubinemia, and the disease that its intraoperative finding was non-appendicitis or normal appendectomy.

Data were analyzed using SPSS 24 software (SPSS Inc., Chicago, IL, USA), descriptive statistics, and Mann-Whitney, Chi-square, and logistic regression tests. For all analyses, $P < 0.05$ was considered statistically significant.

3. RESULTS

Among 100 patients aged between 28.5 ± 14.8 , 48% were men, and the rest were women. Half of the patients with uncomplicated appendicitis were suffering from perforated appendicitis, and half from gangrene appendicitis. Nonparametric tests were used to analyze these data, given that the normality tests showed abnormalities in total bilirubin level variables, leukocytosis, and time of

symptom onset.

The frequency of complicated appendicitis was 58% in men and 42% in women, and there was no significant difference between the two sexes ($P>0.05$).

Based on the Mann-Whitney test, the average total bilirubin level and leukocytosis level were statistically significant in complicated and uncomplicated cases ($P<0.01$) (Table 1). The time of symptom onset was statistically significantly high in complicated appendicitis compared with the control group ($P=0.02$).

The results of this study indicate that 80% of patients with complicated appendicitis and 56% with uncomplicated appendicitis were suffering from leukocytosis, which was statistically significant ($P=0.01$). In other words, the chance of developing leukocytosis in patients with complicated appendicitis is about 3.1 times more than in

patients with uncomplicated appendicitis (Table 2).

The results also showed that serum levels of leukocytosis were not significantly different in subjects with normal and abnormal bilirubin levels. It is noteworthy that 78% of patients with complicated appendicitis and 30% of patients with uncomplicated appendicitis had abnormal bilirubin levels, which were statistically significant ($P=0.001$). The chance of developing abnormal bilirubin levels in patients with complicated appendicitis is about 8.3 times more than in those with uncomplicated appendicitis (Table 3).

Logistic regression analysis for types of appendicitis and independent variables of age, sex, the onset of symptoms at hospital admission, WBC count, and preoperative total bilirubin level was performed employing the Forward method. It is noteworthy that age and sex variables were not significant ($P>0.05$), and other variables

Table 1. Comparison of the variables mean based on the appendicitis type.

Variable	Appendicitis Type		P-value*
	Uncomplicated	Complicated	
Bilirubin level	1.08±0.37	1.83±0.92	0.001
WBC	12.07±4.26	14.72±4.59	0.007
Time of symptom onset	38.04±20.98	46.08±19.89	0.02

Note: * $P<0.05$ was considered as statistically significant.

Table 2. The frequency distribution of appendicitis type based on patients suffering from leukocytosis.

Group	WBC		-	P-value*
	No Leukocytosis	Leukocytosis		
Uncomplicated	22(44%)	28 (56%)	-	-
Complicated	10 (20%)	40 (80%)	3.1	0.01

Note: * $P<0.05$ was considered as statistically significant.

Table 3. The frequency distribution of appendicitis type based on bilirubin levels.

Variable	Appendicitis Type		-	P-value*
	Uncomplicated	Complicated		
Normal Bilirubin Levels	35 (70%)	11 (22%)	-	-
Abnormal Bilirubin Levels	15 (30%)	39 (78%)	8.27	0.001

Note: * $P<0.05$ was considered as statistically significant.

Table 4. The results of multivariable logistic regression analysis of variables associated with occurrence of complicated appendicitis.

P-value*	Exp(β)	Wald	(coefficient) β	Variable
<0.001	-	21.52	-7.14	Constant
<0.001	16.43	17.18	2.80	Total Bilirubin
0.009	1.18	6.89	0.16	WBC
0.04	1.03	4.16	0.02	Time of symptom onset

Note: * $P<0.05$ was considered as statistically significant.

such as WBC level, total bilirubin, and duration of symptom onset remained constant in the model. The odds ratios with significant levels are reported in Table 4.

4. DISCUSSION

This study was performed to determine the relationship between serum bilirubin level and type of appendicitis to find a factor for early diagnosis and correct surgical intervention to reduce morbidity caused by appendicitis complications. Elevated levels of bilirubin are a new diagnostic tool that accurately supports the diagnosis of uncomplicated appendicitis and predicts the complications of appendicitis [14]. In the present study, the odds ratio of developing complicated appendicitis in men was 1.9 times more than in women, but there was no statistically significant difference between the frequency of complicated appendicitis in men and women (58%, 42%). The study conducted by Parsa *et al.* (2012) showed that the frequency of appendicitis (73.5%) was higher in men than in women (26.4%) [8]. In our study, the relationship between total serum bilirubin level and type of appendicitis was investigated, and we found that the chance of developing abnormal bilirubin levels in patients with complicated appendicitis was significantly higher than in the control group.

The results showed that the type of appendicitis was significantly correlated with the bilirubin level. In several studies by Souza *et al.* (2013), Madhvan, and Raman (2019) hyperbilirubinemia was seen in patients with complicated appendicitis, and this relationship was statistically significant [11, 14]. Another study on 538 patients with a history of acute appendicitis showed that serum bilirubin level in patients with perforated appendicitis was significantly higher than that in patients with non-perforated appendicitis [15]. Ambre *et al.* (2018) divided the pathological results into four independent groups (acute appendicitis, suppurative appendicitis, chronic appendicitis, and normal appendicitis). Then, their results showed that there was a significant difference between the four groups in terms of mean total bilirubin level [13].

In our study, the results of multivariable logistic regression showed that total bilirubin level can elevate the chance of developing complicated appendicitis 16.4 times more than from uncomplicated appendicitis. Similar to these results, in the Naya *et al.* (2020) study, total bilirubin was the only factor that showed a significant association with the diagnosis of gangrenous appendicitis with an odds ratio of 3.04 [16]. The level of WBC was significantly higher in patients with complicated appendicitis. Consistent with the present study, Nomura *et al.* (2014) found that patients with gangrene appendicitis had a higher preoperative WBC level than the non-gangrene group [4].

Muller *et al.* (2015) reported that 95% of patients with perforated appendicitis had abnormal WBC [17]. Also, the results of Emmanuel *et al.* (2011) study on the diagnostic value of serum markers in acute appendicitis showed that levels of white blood cells, bilirubin, and C-reactive protein

were higher in patients with perforated appendicitis than patients with non-perforated appendicitis [18].

On the other hand, our results showed no significant difference in serum levels of leukocytosis in patients with normal and abnormal bilirubin levels. In this regard, our results were inconsistent with the Nomura *et al.* (2014) study, which reported that the level of leukocytosis in patients with abnormal bilirubin was significantly higher than that in patients with normal bilirubin [4]. The difference in the duration of symptoms in patients with complicated and uncomplicated appendicitis has been reported in some studies. In the present study, the results also showed that the duration of symptoms in patients with complicated appendicitis was longer than that in patients with uncomplicated appendicitis, which is consistent with the findings of Atahan and Nomura [4, 19]. Finally, logistic regression analysis, including age, sex, time of symptoms onset to hospital admission, WBC count, and pre-operative STB level, was performed. After eliminating the effect of confounding variables (age and sex), the results showed that the onset of symptoms until hospitalization, preoperative leukocytosis, and total bilirubin level were significant variables for the diagnosis of complicated appendicitis in suspected patients. Atahan *et al.* (2011) have reported similar results [19]. Chambers *et al.* (2015) also reported the effect of bilirubin level, WCC, and CRP variables to be significant for predicting perforated/gangrenous appendicitis [20].

CONCLUSION AND RECOMMENDATIONS

Based on the findings, it can be concluded that patients with complicated appendicitis (gangrene, perforation, *etc.*) have higher total bilirubin levels than patients with uncomplicated appendicitis. Patients with hyperbilirubinemia and clinical symptoms of appendicitis should be considered as more probable cases of perforation than those with normal bilirubin levels. Therefore, it can be suggested that serum total bilirubin level should be evaluated as a test alongside WBC, and it can be used to identify complicated appendicitis and decide on the type of surgical approach. It should be noted, however, that the diagnosis of appendicitis is still based on clinical symptoms and examination, and laboratory tests are purely helpful and are not preferred over the surgeon's favor.

LIMITATIONS OF THE STUDY

It requires caution in the field of interpretation and generalization of research findings. Among the limitations of this research, we can point out the small size of the research population, which reduces the generalizability of the findings. Additionally, other psychosocial variables that can directly or indirectly affect the results of the research were not evaluated. To address these limitations, it is suggested that the research should be carried out on a larger scale and with a larger number of samples in multiple hospitals.

AUTHORS' CONTRIBUTION

It is hereby acknowledged that all authors have accepted responsibility for the manuscript's content and consented to its submission. They have meticulously reviewed all results and unanimously approved the final version of the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This article is the result of a research project approved by Jiroft University of Medical Sciences, Iran which is approved by the code of ethics IR.JMU.REC.1400.078.

HUMAN AND ANIMAL RIGHTS

All human research procedures followed were in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2013.

CONSENT FOR PUBLICATION

Informed consent was obtained from the study participants.

STANDARDS OF REPORTING

STROBE guidelines have been followed.

AVAILABILITY OF DATA AND MATERIALS

The data of current study are available from author, [S.D], on a reasonable request. The authors confirm that the data supporting the findings of this study are available within the manuscript.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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