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Hyperbilirubinemia as a diagnostic marker in gangrene or perforation of acute appendicitis

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ABSTRACT

Background. Although several scoring systems are available for the diagnosis of acute appendicitis, there is no one specific for the diagnosis of gangrenous or perforated appendicitis. This study aims to evaluate the sensitivity and specificity of serum total bilirubin in gangrene or perforated appendicitis. *Materials and Methods.* A prospective study was conducted on 55 patients undergoing emergency appendectomy, in whom total serum bilirubin was determined for statistical analysis. *Results*. In our study, out of 55 patients with a perforated or non-perforated appendix, the mean total serum total bilirubin was 2.34 and 1.27, respectively. The cut-off value of serum total bilirubin in this study was calculated using the ROC curve and found to be 1.75. Hyperbilirubinemia is 92.7% sensitive and 96.4% specific in perforation or gangrene of acute appendicitis. The positive predictive value was 96.2% and the negative predictive value was 93%. *Conclusion*s. Patients with acute appendicitis and increased bilirubin levels have a higher chance of gangrene or perforation than those with normal bilirubin levels. Estimation of total serum bilirubin is available in most centers at minimal cost, and can therefore be used in conjunction with clinical and laboratory investigations for the diagnosis of gangrenous or perforated appendicitis.

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Introduction

Acute appendicitis is one of the most common emergencies requiring surgery, so appendectomy is one of the most frequently performed emergency surgeries [1-3]. Appendicitis can be diagnosed clinically and supported by laboratory findings and ultrasonography. Diagnosis of appendicitis is simple in the majority of cases. Many diagnostic scoring systems are available considering symptoms, signs, and laboratory investigations, such as the Alvarado score [4], Appendicitis Inflammatory Response (AIR) score [5], and, for paediatric patients, the modified Alvarado score [6] and Paediatric Appendicitis Score (PAS) [7]. For Asian patients, the Raja Isteri Pengiran Anak Saleha Appendicitis (RIPASA) scoring system is also used [8,9]. None of the above scoring systems can be used for diagnosing appendicitis with gangrene or perforation.

Non-surgical treatment of simple appendicitis is feasible with antibiotics and supportive measures [10-13], but early identification and immediate management of the perforation is crucial for life-saving. With simple appendicitis, the mortality is reported to be 0.3%, but for perforated cases, this increases to about 6% [9]. Early identification and management of the perforation/gangrene are of prime importance in the outcome of a patient with appendicitis. The advantage of serum total bilirubin for predicting acute appendicitis and perforation has been proven in several studies [14-17]. Some other studies suggest bilirubin cannot predict the perforation of appendicitis, including Ghimire et al. [18]. Conflicting information on serum bilirubin green-lights further studies as its estimation is cheap and available in most laboratories. Although several studies indicate the value of serum bilirubin estimation for the prediction of appendicitis with perforation, most are retrospective, lack detailed pre-admission history, do not exclude patients with pre-existing hepatic and hemolytic disease, and lack the final diagnosis in cases of negative histopathology report. Therefore, this prospective study was conducted.

The purpose of this study was to determine sensitivity and specificity of serum total bilirubin in predicting acute gangrenous or perforated appendicitis, thus providing additional data for early intervention to reduce morbidity and mortality of such cases.

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Materials and Methods

This prospective study began after the Institutional Research Committee and Institutional Ethics Committee provided approval. Details of patients undergoing emergency appendicectomy were entered in the proforma by the investigator, including patient age, sex, history, symptoms, disease duration, and hospital stay, preoperative laboratory findings, radiological investigations, and surgical findings. The subjects were randomly sampled into two groups of acute appendicitis cases with perforation or gangrene and acute appendicitis cases without perforation or gangrene. The study period was from January 2018 to June 2019. We enrolled 110 patients into two groups (55 each) of perforated and non-perforated appendicitis.

Inclusion and exclusion criteria

Patients attending the emergency department with the clinical diagnosis of appendicitis were selected. A detailed history and clinical examination were done. A laboratory investigation and ultrasound scan were done for all cases, and CT scans were done when the clinical findings did not match the laboratory or USG findings. Patients undergoing emergency appendicectomy were included in the study.

All patients with a documented history of jaundice or conditions causing jaundice, like alcoholism, liver disease, hemolytic disease, acquired or congenital biliary disease, cholelithiasis, choledocholithiasis, cancer of the hepato-biliary system, or multiple recent blood transfusions were excluded. The subjects were divided into two groups: acute appendicitis with perforation or gangrene and acute appendicitis without perforation or gangrene. Data were then coded and entered into an Excel spreadsheet.

Statistical tests used

Categorical and quantitative variables were expressed as frequency (percentage) and mean ± SD, respectively. The independent t-test was used to compare quantitative parameters between categories. The Chi-square test was used to find an association between categorical variables. Receiver Operating Characteristic (ROC) graphs were plotted, and the area under the curve was calculated to assess the diagnostic accuracy of serum total bilirubin in detecting gangrene or perforation in acute appendicitis and the optimal cut-off scores. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were calculated for the diagnostic accuracy of serum total bilirubin in detecting gangrene or perforation in acute appendicitis. For all statistical interpretations, $p < 0.05$ was considered the threshold for statistical significance. Statistical analyses were performed using a statistical software package SPSS, version 20.0

Results

Appendectomy was performed in all age groups, most frequently at 20–30 years, followed by 10–20 and 30–40 years (Figure 1). The age difference between perforated and non-perforated cases was non-significant ($p = 0.184$).

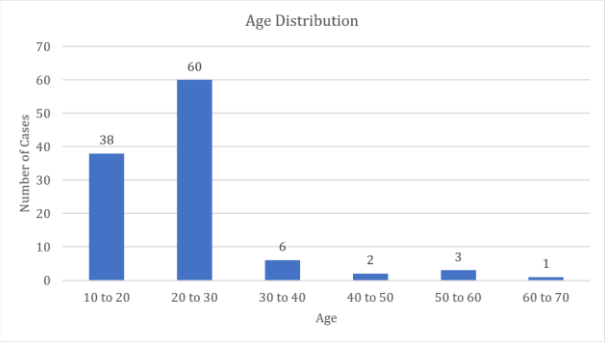

Figure 1. Age distribution (n = 110)

Out of the 55 non-perforated cases, 33 (60%) were males and 22 (40%) were females. Of the 55 perforated cases, 34 (62%) were males and 21 (38%) were females. Even though a slight male predominance was noted in the distribution of perforated and non-perforated cases, this difference was non-significant in a chi-square test. There was no difference between the occurrence of perforation in males and females in our study (Table 1).

Table 1. Male - Female distribution (n = 110)

Sex	Male	Female	Total
Perforated Cases	34 (62%)	21 (38%)	55
Non-perforated Cases	33 (60%)	22 (40%)	55
Total	67 (61 %)	43 (39%)	110

The duration of symptoms was then analyzed. The mean duration of symptoms for both perforated and non-perforated cases was 1.6, with a standard deviation of 0.8. This association between the duration of symptoms in perforated and non-perforated cases was non-significant ($p = 0.184$).

Of 55 cases of a perforated appendix, 48 patients had a fever, and seven patients had no fever. Of 55 non-perforated cases, 27 patients had a fever and 28 patients did not. This difference was statistically significant via a chi-square test ($x2 = 18.48$, $p < 0.01$). We found that the chance of perforation was higher in patients having fever compared to patients with no fever. The mean hospital stay was 7.3 with a standard deviation of 0.9 in perforated cases and 4.2 with a standard deviation of 0.8 in non-perforated cases. This difference in hospital stay among perforated and non-perforated cases was found to be statistically significant ($p < 0.01$).

From 55 cases of a perforated appendix, 18 patients had USG findings of a perforated appendix, 28 patients had a USG report suggestive of inflamed appendix without perforation, and nine patients had a normal USG. Of the 55 non-perforated cases, four had USG findings suggestive of a perforated appendix, 36 patients had USG finding suggestive of inflamed appendix without perforation, and 15 patients had USG findings with no evidence of inflamed appendix. This result was statistically significant ($x2 = 0.41$, $p = 0.003$ ($p < 0.01$)).

The mean pulse rate was 96 with a standard deviation of 10.2 in perforated cases and 87.8 with a standard deviation of 10.6 in non-perforated cases. This difference was statistically significant ($p < 0.01$).

In our study, the mean total leucocyte count of perforated cases was 19,272.7 with a standard deviation of 2,258. For non-perforated cases, it was 13,294.5 with a standard deviation of 1,143. This difference was significant ($p < 0.01$). That is, the total leucocyte count among perforated cases was higher than in non-perforated cases, indicating that the risk of perforation increases as total leucocyte count increases in cases of acute appendicitis.

The mean SGOT in cases of a perforated appendix was 70.7 with a standard deviation of 16.1 and 34 with a standard deviation of 10 in non-perforated cases. This difference in the value of SGOT between perforated and non-perforated cases was statistically significant ($p < 0.01$). Patients with acute appendicitis with serum SGOT higher than normal can have a perforated appendix. We found the mean SGPT was 67.7 with a standard deviation of 18.3 for perforated cases and 33.8 with a standard deviation of 13.5 for non-perforated cases. This difference was found to be statistically significant ($p < 0.01$). For the patients with a perforated appendix the mean serum total bilirubin was 2.34, and in the non-perforated cases it was 1.27. Our study found that serum total bilirubin level was higher in cases of perforation compared to cases without perforation (Table 2, Figure 2).

Table 2. Accuracy of serum total bilirubin in diagnosis of acute gangrenous or perforated appendicitis (n = 110)

Serum Total Bilirubin	Group		Total
	Case	Control	
>=1.75	51	2	53
<1.75	4	53	57
Total	55	55	110

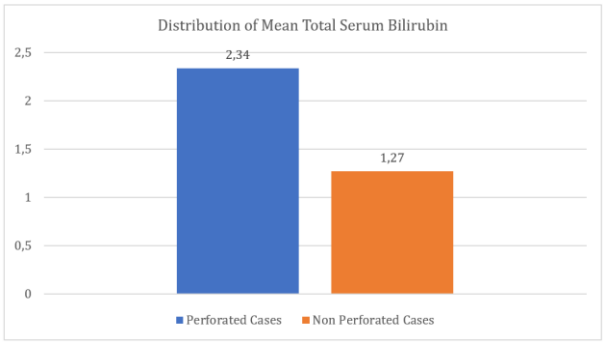

Figure 2. Distribution of Mean Serum Total Bilirubin (n = 110)

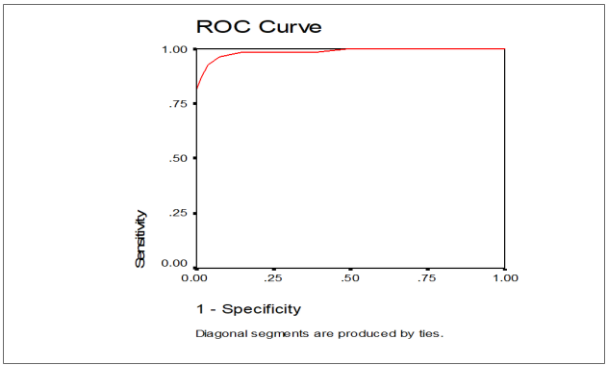

Figure 3. Diagnostic accuracy of serum total bilirubin in diagnosing gangrene or perforation in acute appendicitis cases admitted

The cut-off value of serum bilirubin calculated using the ROC curve was 1.75. The area under the curve was 0.986, with a standard deviation of 0.009, which was statistically significant. Area Under the curve = 0.986 (0.968 – 1.004), $p < 0.001$, best cut off = 1.75 (Figure 3).

Table 3. Comparison of background characteristics of patients (* denotes 't' value)

		Case		Control		χ^2	p-value
		Count	Percent	Count	Percent		
Fever	Yes	48	87.3	27	49.1	18.48	< 0.01 (significant)
	No	7	12.7	28	50.9		
Pulse Rate	Normal	40	72.7	49	89.1	4.77	0.029 (significant)
	Increased	15	27.3	6	10.9		
	Mean ± SD	96 ± 10.2		87.8 ± 10.6			
TC	Normal	0	0.0	0	0.0	17.52*	< 0.01 (significant)
	Increased	55	100.0	55	100.0		
	Mean ± SD	19272.7 ± 2258		13294.5 ± 1143			
SGOT	Normal	1	1.8	32	58.2	41.6	< 0.01 (significant)
	Increased	54	98.2	23	41.8		
	Mean ± SD	70.7 ± 16.1		34 ± 10			
SGPT	Normal	3	5.5	30	54.5	31.56	< 0.01 (significant)
	Increased	52	94.5	25	45.5		
	Mean ± SD	67.7 ± 18.3		33.8 ± 13.5			
USG	No inflamed appendix	9	16.4	15	27.3	11.41	0.003 (significant)
	Inflamed appendix without perforation	28	50.9	36	65.5		
	Inflamed appendix with perforation	18	32.7	4	7.3		
Hospital Stay	3 – 5	1	1.8	52	94.5	18.95*	0.01 (significant)
	6 – 7	34	61.8	3	5.5		
	8 – 10	20	36.4	0	0.0		
	Mean ± SD	7.3 ± 0.9		4.2 ± 0.8			

The following data were obtained in our study: a sensitivity of 92.7%, specificity of 96.4%, a false negative rate of 7.3%, a false positive rate of 3.6%, a positive predictive value of 96.2%, a negative predictive value of 93.0%, a positive likelihood ratio of 25.5, and a negative likelihood ratio of 0.1.

Table 4. Comparison of background characteristics of patients (* denotes 't' value)

		Case		Control		χ^2/t	p-value
		Count	**Percent**	**Count**	**Percent**		
Age	≤20	23	41.8	15	27.3	1.34*	0.184 (non-significant)
	21 - 25	19	34.5	24	43.6		
	26 - 30	7	12.7	10	18.2		
	> 30	6	10.9	6	10.9		
	Mean ± SD	23.1 ± 7.8		25.3 ± 9			
Sex	Male	34	61.8	33	60.0	0.04	0.845 (non-significant)
	Female	21	38.2	22	40.0		
Duration	1	31	56.4	30	54.5	1.34*	0.184 (non-significant)
	2	18	32.7	19	34.5		
	3 - 4	6	10.9	6	10.9		
	Mean ± SD	1.6 ± 0.8		1.6 ± 0.8			

Discussion

Scoring systems for appendicitis usually utilize signs, symptoms, laboratory investigations, and imaging studies. No single test can diagnose appendicitis. Diagnosis must consider history, examination findings, laboratory investigation, and imaging studies. The CT scan is reliable in diagnosing appendicitis or perforation, but has limited availability, carries the risk of radiation, especially in those of child-bearing age, and is costly. Moreover, some studies have shown that it does not reduce the negative appendicectomy [19,20]. In diagnosing appendicitis, laboratory tests are chosen based on their availability, low cost, minimally invasive nature, and repeatability [21]. Serum total bilirubin satisfies all of these criteria.

Sepsis leading to jaundice is well established. Bacteria, especially gram-negative strains, are a common causative agent. Increased hemolysis is associated with several bacteria, including Escherichia Coli. Other causes include reduced bilirubin uptake induced by endotoxins and cholestasis produced by inhibited bile salt transport mediated by cytokines produced by bacterial endotoxins. The pathophysiology of increasing bilirubin in response to intra-abdominal infection is transient portal pyemia and inflammatory-mediated cholestasis [22].

Of the 110 patients who underwent emergency appendicectomy in our study period, the most commonly reported age group was those under 20-30 and the least was those aged 60-70 years. We found a slight male preponderance in both the perforated (62:38) and non-perforated (60:40) cases. The distribution of age and sex in our study was similar to the recent work by Sarla et al. They found that the incidence of acute appendicitis is more common in males (63.76%) compared to females (36.23%) and in those aged 20-30 years (39.13%) [23].

The mean duration of symptoms in both perforated and non-perforated cases was 1.6. In the perforated and non-perforated groups, 48 out of 55 (87%) and 28 out of 55 (51%), respectively, reported fever, indicating a higher likelihood of perforation in patients with fever compared to patients with no fever. In our study, among the perforated cases, the mean hospital stay was 7.3 compared to 4.2 in non-perforated cases. This is similar to a study by Kearney et al., which concluded that the chance of complications increases the hospital stay [24]. Analyzing the pulse rate of 110 patients in this study revealed no significant difference in pulse rate between perforated and non-perforated cases, although perforated cases had a slightly higher pulse rate compared to non-perforated cases.

The mean total leucocyte count in the 55 perforated appendicitis cases was 19,272.7, while in 55 non-perforated cases it was 13,294.5, and this difference was statistically significant. This reflects a greater chance of perforation in those with elevated total leucocyte counts. This is comparable with a study by Guraya et al. in 237 patients which found that high WBC with a differential count is a predictable indicator of the severity of appendicitis and signifies a more advanced disease stage [25].

The serum SGOT levels in perforated and non-perforated cases were 70.65 and 33.98, respectively, and this difference was statistically significant. This is similar to a study by Beltran et al. [26]. The serum SGPT level in perforated and non-perforated cases were 67.73 and 33.76, respectively, and this difference was statistically significant. Research by Motie et al [27] provided similar results. The raised mean serum total bilirubin levels in perforated cases was 2.345 and 1.273 in non-perforated cases. Our study found that the serum total bilirubin level

was raised much higher in perforation than in cases of no perforation. Ramasamy et al. and Kumar et al. had similar results [28, 29].

The sensitivity, specificity, positive predictive value, and negative predictive value of serum total bilirubin levels in gangrene or perforation of appendicitis were 92.7%, 96.4%, 96.2%, and 93%, respectively. Beltran et al. [26] and Khan et al. [30] had similar results. The high specificity of total serum bilirubin guides the clinician in suspecting the perforation and adopting a rapid and appropriate treatment.

Conclusions

Hyperbilirubinemia in patients with appendicitis should raise suspicion of gangrene or perforation compared to patients with normal bilirubin levels. An increase in serum total bilirubin levels can be used corroborative to clinical, laboratory, and sonological findings, especially with equivocal results. This methodology is widely available at a minimal cost.

It is highly useful in the management of appendicitis, especially in areas with poor resources and lacking facilities for CT scans or other imaging modalities. An early appendectomy can be considered to significantly reduce morbidity and mortality. Consequently, the serum total bilirubin level should be a part of the basic assessment of appendicitis.

Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

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