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## **To Determine the Diagnostic Accuracy of Raised Serum Bilirubin in Predicting Acute Appendicitis Taking Post-Operative Histopathology as the Gold Standard**

<sup>1</sup> Dr. Maaz Bin Altaf, <sup>2</sup> Dr. Asad Farooq, <sup>3</sup> Dr. Muhammad Yasir Jan, <sup>4</sup> Dr. Saad Ul Khaliq, <sup>5</sup> Dr Athar Ahmad, <sup>6</sup> Dr. Komal Qayyum, <sup>7</sup> Dr. Warda Batool Nadeem

<sup>1,2,3</sup> Medical Officer, District Headquarters Hospital, Department of Health, Peshawar Pakistan

<sup>4,5</sup> Post Graduate Resident, Department of Surgery, Northwest General Hospital, Peshawar, Pakistan

<sup>6</sup> Department of Medicine, North West General Hospital, Peshawar, Pakistan

<sup>7</sup> Medical Officer, North West General Hospital, Peshawar, Pakistan

Corresponding Author: **Dr. Maaz Bin Altaf**

### **Abstract**

#### **Objective:**

To determine the diagnostic accuracy of raised serum bilirubin in predicting acute appendicitis taking post-operative histopathology as the gold standard.

**Study Design:** Cross sectional Validation

**Study Duration:** May 14, 2019 to Nov 13, 2019

#### **Material and Methods**

After taking permission from the hospital ethical committee all the patients presenting with symptoms of abdominal pain that migrates to right iliac fossa, anorexia, nausea, vomiting, fever, tenderness in the right iliac fossa, rebound tenderness in the right iliac fossa and fulfilling the inclusion criteria were admitted in surgical unit through OPD and Emergency Department. Complete baseline investigations including total serum bilirubin were done prior to surgery and readings were noted. Post operatively the appendix specimen were

collected, preserved in formaline solution and sent to a single expert histopathologist. The patient's histopathology reports were followed up for in out patient department.

#### **Results:**

184 patients with suspected appendicitis had observed. Male to female ratio 1.19:1. Average age was 28.27 years+9.06SD. Majority of the appendicitis 124(67.39%) were confirm through histopathology while on 60(32.61%) were not confirmed as acute appendicitis. Over all the diagnostic accuracy of serum bilirubine in diagnosis of acute appendicitis is 80.98%.

#### **Conclusion:**

Serum bilirubin can be considered as a vital tool for the diagnosis of acute appendicitis. In situations where this investigation is normal, further evaluation needs to be done in the form of an ultrasound or diagnostic laparoscopy.

**Keywords:** Acute Appendicitis, Serum Bilirubin, Appendicectomy, Sensitivity, Specificity

### **Introduction**

Appendicitis is the most common cause of abdominal pain and the most common surgical condition requiring emergency surgery [1, 2]. It is estimated that around 7% of population undergoes appendectomy in their lifetime [1]. Another study suggests that out of those who were operated on, 53% were found to have acute appendicitis [3]. It is mainly a disease of young people with 40% of cases occurring in age range of 10 to 29 years [4]. The treatment of choice for appendicitis is surgery [5] but conservative management with antibiotics for relatively mild cases is also in practice [6].

Appendectomy is known to be the most commonly performed surgery around the world [1] but its accurate diagnosis is still very difficult [5]. This is the reason why negative appendectomies range from 5% to 40% [7] depending upon experience of the clinicians. Diagnosis is mainly based on the history of pain in the right iliac fossa [7, 8]. There is no single test that can be used to diagnose acute appendicitis but there are different scoring systems used for this purpose [1, 5, 9]. Alvarado score being the most commonly used one [1, 9]. Surgery is done in the immediate possibility when there is a hint of diagnosis and not delayed for it to become certain [5, 8]. As a delay can cause further complications such as gangrenous or perforated appendix [5, 8].

High white cell count has been described as the most effective tool in diagnosing acute appendicitis in the presence of suggestive history and clinical symptoms [10]. Many cases of acute appendicitis may not have the typical presentation which can lead to a misdiagnosis [2, 9] and delay surgery leading to complications. Around 16.5% of acute appendicitis cases become complicated mainly due to delayed presentation, presenting as perforated or gangrenous appendix [5]. Appendix can perforate within 48 hours of onset of the disease if ignored [8].

Better diagnostic tools and scoring systems need to be devised so that negative appendectomies as well as complicated ones that present due to delayed diagnosis can be prevented [7]. Many studies have been conducted in the recent past showing that some of the blood markers and their raised values are of some utility, such as white cell count, C-reactive protein and serum bilirubin [2, 5]. Radiological assistance has also been tried in diagnosing acute appendicitis such as ultrasound scans, C.T scans and MRI [1, 2, 5, 9]. But they have their own downsides. They expose the patient to high radiations, are time taking and expensive [1, 5, 9]. They may also not be available in emergency setups [1].

There is a need of non-invasive, inexpensive diagnostic criteria that can help in diagnosis [5]. In recent years quite a number of studies have been conducted to show elevated levels of serum bilirubin as the diagnostic tool for acute appendicitis and also its utility as a severity indicator [1, 5, 7, 9, 10]. A study showed the mean value of total bilirubin to be 8umol/l in patients who didn't have acute appendicitis on histopathology while it was raised in those with confirmed acute appendicitis being 13umol/l and even higher i.e 17umol/l in those with perforated appendicitis. 15umol/l being the cut-off value the sensitivity of raised bilirubin in predicting acute appendicitis was shown to be 50% and specificity was 68% while for perforated appendicitis sensitivity was 65% and specificity 68% [2].

In many setups the exhausted man-power tries to reduce the surgical procedures at night, often delaying the less severe cases. In this case it is important to know about the severity of the case, as delaying a normal appendectomy for 12 to 24 hours will not increase complications. But if it is already complicated then immediate surgery is required. Secondly in our setups patients often consult the quacks in peripheries before coming to hospital, who give them potent analgesics which mask the true clinical picture making diagnosis difficult. Therefore, a highly sensitive and specific blood marker is required that can act as a diagnostic tool. As there is no individual blood marker that can alone be relied upon right now. White cell count and C-reactive protein are widely in use but cannot be completely relied upon as cases with short history may not show raised C- reactive protein and cases of acute appendicitis with normal white cell count are commonly encountered and any inflammatory reaction can cause these blood markers to rise. This study specifically emphasizes upon the role of raised serum bilirubin in diagnosing acute appendicitis and is intended to calculate its diagnostic accuracy preoperatively against the post operative histopathology.

### Objective

To determine the diagnostic accuracy of raised serum bilirubin in predicting acute appendicitis taking post-operative histopathology as the gold standard.

### Operational Definitions

**Suspected Acute Appendicitis:** Any patient coming with a history of right iliac fossa were assessed using the Alvarado/MANTRELS score. A score of  $\geq 7$  was labeled as positive but if  $< 7$ , then were labelled as negative.

**Mantrels Score:** M=Migratory pain (An unpleasant sensation starting in the area around umbilicus then migrating to right iliac fossa), A=anorexia, N=nausea,

T=tender right iliac fossa (Grimacing or expressing discomfort on deep palpation of right iliac fossa), R=rebound tenderness (Grimacing or expressing discomfort on quickly withdrawing hand after deeply palpating right iliac fossa), E=elevated temperature (Temperature of 99F or more), L=Leucocytosis (Leucocyte count more than 11000X10<sup>9</sup>), S=shift to left (Neutrophils more than 75% of total leucocytes in a blood sample). T and L carry 2 points each while rest of the letters carry 1 each in scoring Mantrels.

**Acute Appendicitis:** On post-operative histopathology dense neutrophilic infiltration of muscularis propria with congestion and edema of the wall of appendix was labeled as positive.

**Elevated Total Serum Bilirubin:** Total serum bilirubin values of more than 15umol/l Or 0.88mg/dl.

**True Positive (TP):** When patient's preoperative total serum bilirubin value is more than 1.2mg/dl and then is confirmed positive on histopathology.

**True Negative (TN):** When patient's preoperative total serum bilirubin value is 1.2mg/dl or less and is also negative on histopathology.

**False Positive (FP):** When patient's preoperative total serum bilirubin value is more than 1.2mg/dl but is negative on histopathology.

**False Negative (FN):** When patient's preoperative total serum bilirubin value is 1.2mg/dl or less but is positive on histopathology.

**Sensitivity:** TP / (TP+FN)

**Specificity:** TN / (TN+FP)

**Positive Predictive Value (PPV):** TP / (TP+FP) Negative

**Predictive Value (NPV):** TN / (TN+FN)

### Materials and Methods

**Study Setting:** Department of surgery in Khyber Teaching Hospital Peshawar.

**Study Duration:** May 14, 2019 to Nov 13, 2019

**Sample Size:** Sample size was 184, keeping 53% as the frequency of acute appendicitis, sensitivity of raised serum bilirubin being 50% and specificity 68%, 10% absolute precision and 95% confidence interval using online software for sensitivity and specificity.

**Study Design:** Descriptive comparative cross-sectional study.

**Sampling Technique:** Non-probability consecutive sampling.

### Sample Selection

**Inclusion Criteria:** Age 15 to 50 years Male sex

Female sex

Patients presenting with pain in right iliac fossa and MANTRELS score 7 or more

**Exclusion Criteria:**

Patients whose appendix was removed during another surgery e.g., as a part of right hemicolectomy etc. Patients with a history of chronic liver disease. Patients who are HBsAg or AntiHCV antibodies positive. Pregnant patients. Patients with a right lower quadrant mass on palpation or confirmed on ultrasound. Patients whose preoperative total serum bilirubin is not recorded.

**Data Collection Procedure**

This study was conducted in Department of Surgery, Khyber Teaching Hospital, Peshawar. Ethical committee’s approval was taken prior to conduction of study. The patients visiting OPD or emergency with right iliac fossa pain and tenderness was evaluated. A detailed history including name, age, address and complete demographics were taken followed by complete physical examination and investigations. Patients who undergo appendectomy were included in the study. An informed written consent were taken from the patient or next of kin. Complete baseline investigations including total serum bilirubin were done prior to surgery and readings were noted. Surgeries were performed on McBurney’s or Lanz incisions by experienced resident surgeons or Fellow surgeons of CPSP. Appendicitis was confirmed on histopathology. All relevant data were recorded on a structured proforma. All inclusion and exclusion criteria were strictly followed to control confounders and bias in study results.

**Data Analysis**

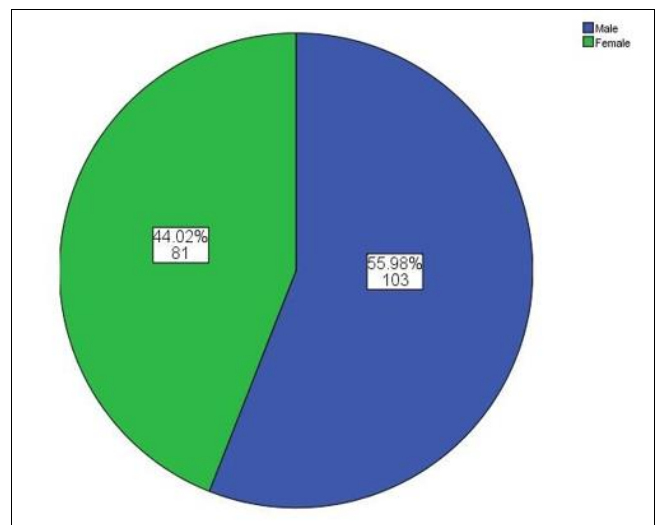
Data were entered and analysed on SPSS version [20]. Frequencies and percentages were calculated for categorical variables like gender, raised serum bilirubin and acute appendicitis on histopathology. Mean and standard deviation were calculated for age, duration of symptoms and serum bilirubin levels. Diagnostic accuracy was calculated for raised serum bilirubin by calculating sensitivity, specificity, positive predictive value, negative predictive value and accuracy. Effect modifiers like age, gender, duration of symptoms were controlled through stratification. Post stratification diagnostic accuracy was computed. Results were displayed in form of tables and charts.

**Results**

In this study, 184 patients with suspected appendicitis had observed through serum bilirubin and underwent open surgery for confirmation. Male were found 103(55.98%) of the patients, while 81(44.02%) have female patients. Male to female ratio 1.19:1 (Fig 1). Patients age was divided in four categories out of which most presented in young age i.e., 21-30 years which was 70(38%) while 47(25.5%) patients having age less than or equal to 20 years, 50(27.2%) were of age range 31-40 years and 17(9.2%) presented at age more than 40 years. The study included age ranged from 15 up to 50 years. Average age was 28.27 years+ 9.06SD. (Table 1) Majority of the appendicitis 124(67.39%) were confirm through histopathology while on 60(32.61%) were not confirmed as acute appendicitis. (Fig 2) Age wise distribution of biopsy results shows that majority of the

appendicitis 35(74.5%) were found in less than or equal to 20 years of age, 44(62.9%) patients have age 21-30 years, 34(68%) have age range of 31-40 years and 11(64.7%) cases have age range of more than 40 years of age. Similarly, 12(25.5%) patients have age less than or equal to 20 years, 26(37.1%) have age 21-30 years, 16(32%) patients have age 31-40 years and 6(35.3%) patients were observed in more than 40 years and were observed as no acute appendicitis. (Table 2).

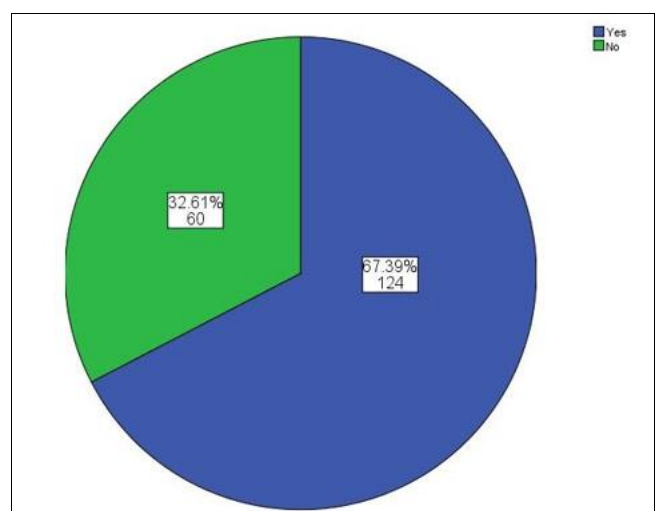
Serum bilirubin plays a key role in diagnosis of acute appendicitis. The sensitivity and specificity of Serum bilirubin in diagnosis of acute appendicitis are 81.45% and 80% respectively while it has positive predictive value of 89.38% and negative predictive value is 67.61%. Over all the diagnostic accuracy of Serum bilirubin in diagnosis of acute appendicitis is 80.98%. (Table 3).



**Fig 1: Gender Wise Distribution**

**Table 1: Age Distribution (in Years)**

	Frequency	Percent	Mean ± SD
<= 20	47	25.5	28.27 years+ 9.06
21 - 30	70	38.0	
31 - 40	50	27.2	
41+	17	9.2	
Total	184	100.0	



**Fig 2: Appendicitis on Histopathology**

**Table 2:** Age Wise Distribution of Biopsy Results

		Appendicitis on Histopathology		Total	P-value
		Yes	No		
Age (in years)	<= 20	35 74.5%	12 25.5%	47 100.0%	0.617
	21 - 30	44 62.9%	26 37.1%	70 100.0%	
	31 - 40	34 68.0%	16 32.0%	50 100.0%	
	41+	11 64.7%	6 35.3%	17 100.0%	
Total		124 67.4%	60 32.6%	184 100.0%	

**Table 3:** Accuracy of Serum Bilirubin in Diagnoses of Acute Appendicitis

		Histopathology		Total
		Positive	Negative	
Serum Bilirubin	Positive	101	12	113
	Negative	23	48	71
Total		124	60	184

Sensitivity 81.45%  
 Specificity 80%  
 Positive predictive value 89.38%  
 Negative predictive value 67.61%  
 Accuracy 80.98%

**Discussion**

Acute appendicitis, despite being more frequently seen in the younger feminine population, is more difficult to diagnose in females as compared to males. One of the reasons cited by experts is that appendicitis and some gynecological disorders have the same clinical presentation hence making appendicitis very difficult to predict and diagnose in clinical surgery. The improvements in accurate prediction of this pathology have been minute recent years [11-13]. The usual combination of a well taken history coupled with physical examination and laboratory investigations achieves a diagnostic accuracy to 80% and when radiology and histopathology is used, the percentage can reach up to 90% [13-17]. In the current study, the mean age of presentation was [28, 27] with majority of the patients lying in the second and third decade of life and the findings are consistent with the study of Jamal s, Amin M, *et al* [18] and Bresciani C, perez RO, Habr-Gama A, *et al* [19]. In series of 190 patients 57% were females and 43% were males by the study of gaitini D, Beck RAZI N *et al* [20].

There are multiple disorders that can give right iliac fossa pain therefore the differential diagnosis of such pain has never been plain sailing [21]. Even though there are a multitude of diagnostic grades [22] and investigation tools such as C-reactive proteins [23], it has always been a challenge for the physician as no laboratory or radiographic test has been regarded as 100% accurate [24].

This study has shown there is a high sensitivity and specificity serum bilirubin 81.45% and 80% respectively with good positive predictive value of 89.38% and high negative predictive value of 67.61% in case of acute appendicitis, and should alert the surgeon regarding the possibility of this diagnosis. Cheekuri *et al* in 2017 conducted a prospective study Hyperbilirubinemia as a predictor of the severity of acute appendicitis- an observational study with sample size of 110 showed results

of sensitivity 94%, specificity 66%, PPV 88.5%, NPV 80%. [25] D’souza *et al* conducted a prospective study Bilirubin; a diagnostic marker for appendicitis with sample size of 143 showed results of sensitivity 70%, specificity 82%, PPV 47%, NPV 93% [26]. Giordino *et al* conducted a meta-analysis Elevated serum bilirubin in assessing the likelihood of perforation in acute appendicitis: a diagnostic meta-analysis including 8 studies with sample size of 4974 showed sensitivity 49%, specificity 82% [27]. One of study study confirms that statistically hyperbilirubinaemia occurs significantly more frequently in patients with perforated appendicitis and non-perforated appendicitis than in those with no appendiceal inflammation. Compared with WBC and CRP, hyperbilirubinaemia shows less sensitivity, meaning it is not useful as a rule-out test for perforated appendicitis. Furthermore, the positive likelihood ratio of serum hyperbilirubinaemia is insufficiently high for use as a reliable rule-in test for perforated or even any appendicitis (perforated and nonperforated) [28, 29].

Only few publications have reported an association between serum bilirubin and appendicitis. A first series of nine patients with appendicitis and jaundice was described by Miller and Irvine [30]. Recent publications described a significant association between hyperbilirubinaemia and perforated appendicitis [31-35]. Sand *et al* [31] showed that patients with hyperbilirubinaemia and symptoms of appendicitis had a greater probability of appendiceal perforation than did those with regular bilirubin levels. Kaeser *et al* [32] confirmed that hyperbilirubinaemia is a statistically significant marker of perforation.

**Conclusion**

The diagnosis of acute appendicitis can be made confidently with history and proper examination. Serum bilirubin can be helpful in the diagnosis of doubtful cases of right iliac fossa pain. When measured together increases their diagnostic value with more reliable positive predictive value than negative predictive value. However, it should be bourn in mind that in conditions such as appendicitis, the severity of the disease and the possibility of perforation are never diagnosed only on the basis of serum laboratory investigations and further confirmation by radiology and histopathology are always warranted.

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