

## Do Serum Markers Help in Diagnosis of Acute Appendicitis??

Dr. Fakhra Noureen<sup>1</sup>, Dr. Ashfaque Ahmed<sup>2</sup>, Dr. Baseer Ullah<sup>3</sup>, Dr. Lyba Ghayour<sup>4</sup>, Dr. Irfan Fazal<sup>5</sup>, Dr. Muhammad Iqbal<sup>6</sup>, Dr. Imran ali<sup>7</sup>

<sup>1</sup>Assistant Professor, Pathology, Al Nafees Madical College, Islamabad

<sup>2</sup>Consultant General Surgeon, Surgical Unit 4, Liaquat University Hospital, Hyderabad

<sup>3</sup>Resident of General Surgery, Mayo Hospital, Lahore

<sup>4</sup>Resident of General Surgery, Mayo Hospital, Lahore

<sup>5</sup>Consultant General Surgeon, Mayo Hospital, Lahore

<sup>6</sup>Resident of General Surgery, Mayo Hospital, Lahore

<sup>7</sup>Resident of General Surgery, Mayo Hospital, Lahore

### **ABSTRACT**

**BACKGROUND:** A complete medical history in conjunction with a medical assessment is usually sufficient to diagnose acute appendicitis. The purpose of this investigation was to see how useful high white cell count (WCC), C-reactive protein (CRP), and bilirubin seeing that analytical indicators for appendicitis.

**METHODS:** Over a three-year period, a retrospective cohort study on individuals who had appendectomy. The figures were compiled, including patient age, gender, blood picture, and appendix histopathology. WCC, CRP, and bilirubin sensitivities, specificity, positives, and negative predictive values were premeditated independently or in grouping for all patients.

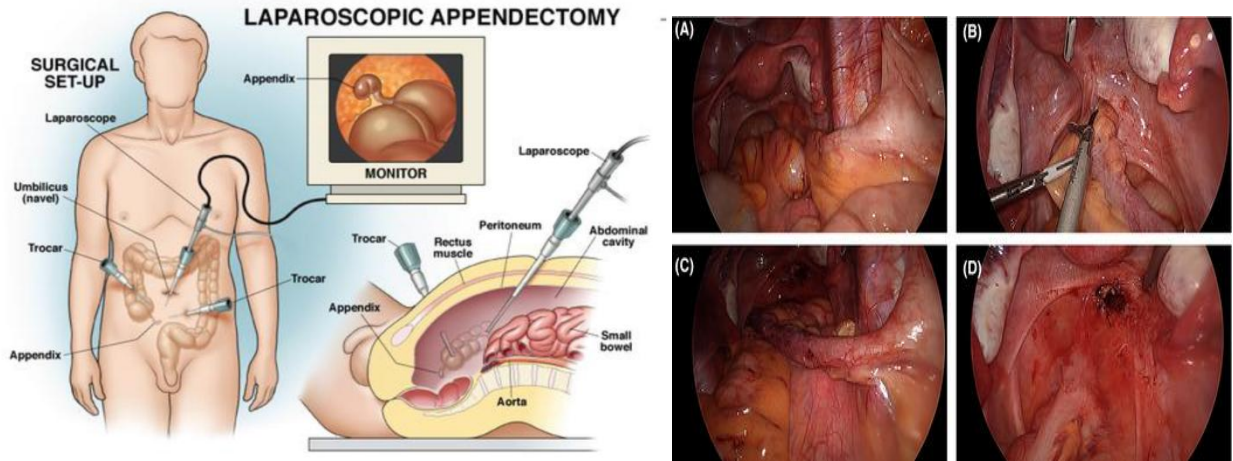
**RESULT:** There were 50 patients in all. In terms of CRP (31 vs 72) p value less than 0.01, mean total WCC (10.8 vs 14.1) p value less than 0.01, and mean bilirubin levels (10.7 vs 17.3), there is a consequential dissimilarities between persons with negative and positive appendicitis

**CONCLUSIONS:** Appendicitis is a complex diagnosis, and blood testing may assist the surgeon in making a choice.

### **INTRODUCTION:**

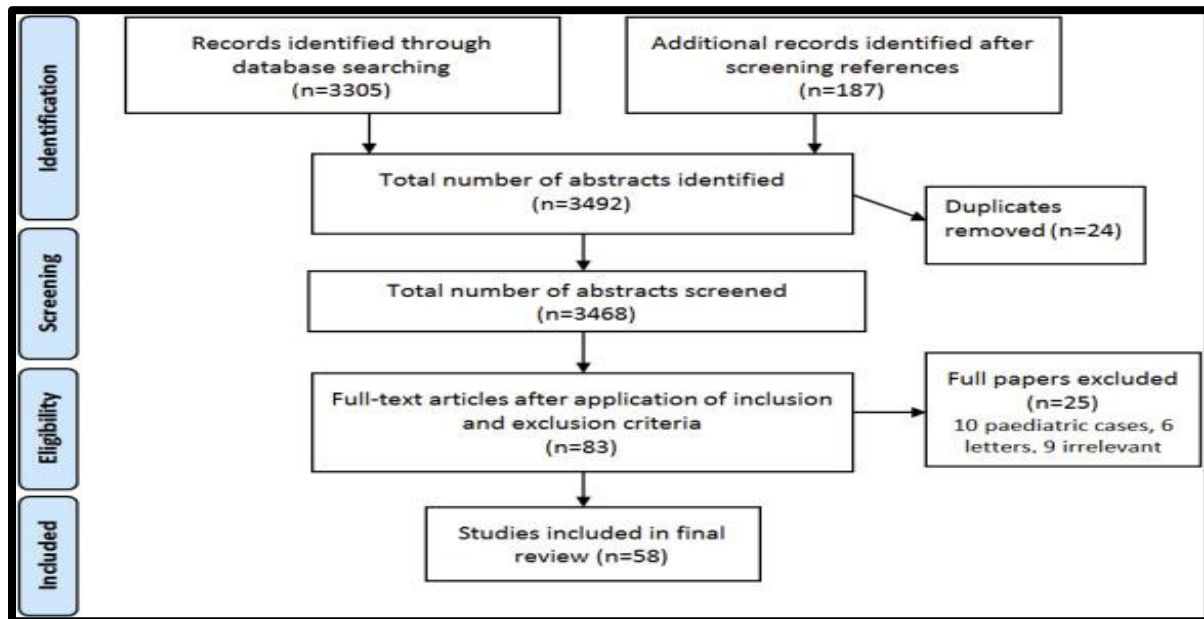
Acute appendicitis is among the frequently encountered operational calamities, and appendectomy continues to be one of the most frequently performed emergency procedures globally. A complete health record, pooled with a medical assessment that elicits the widespread physical symptoms linked with localized peritonitis, is usually sufficient to diagnose acute appendicitis<sup>1</sup>. However, appendicitis is not always easy to diagnose, particularly in girls and women, because a gynaecological pathogenesis may imitate acute appendicitis. Additionally, because the position of appendix may vary, such as concealed or situated behind the cecum appendicitis, patients may not display enough peritoneal symptoms to maintain the verdict of acute appendicitis. There is at present, no dependable explicit marker for intensity of an infected appendix. In spite of innovative and insightful advances, the pace of negative appendectomies

stays somewhere in the range of 15% and 50%. Numerous scoring frameworks for severity an infected appendix have been created. The frameworks, notwithstanding, possess their own impediments, as they were basically utilized on kids and have not been demonstrated to be precise in the grown-up female population<sup>2</sup>. The presence of raised provocative markers, for example, white cell check (WCC) and C-responsive protein, upholds the finding of intensity of infected appendix (CRP). A few examinations, nonetheless, have shown that neither of these markers is analytic or explicit for prediction of appendicitis. The investigators announce that they have no clashing interest<sup>3</sup>.



Currently, it was found that serum bilirubin can help in the analysis of perforated appendix, with an affectability of 70% and particularity of 86%.<sup>1</sup> The precision of infected appendix recognition dependent on hyperbilirubinemia stays obscure. The reason for this examination is to decide the demonstrative utility of raised WCC, CRP, and bilirubin levels in acute appendicitis<sup>5</sup>.

**LITERATURE SEARCH:**



## **METHODOLOGY:**

A retrospective analysis of the following subjects who went through appendectomy at our medical facility over a period of a year was conducted ( April 2020 to April 2021)<sup>4</sup>. Our research division isolate the participants using the terminology "appendicitis," "appendectomy," and "laparoscopic appendectomy." The gathered information relevant to the patient, including age, gender, blood picture (WCC, leukocyte level, CRP, and LFTs including bilirubin), and histopathological result of appendix, were extracted through the research branch and electronic health record of medical facility. Figures were assembled and encapsulated in Microsoft Excel 2010 version. Appendectomy was implemented either laparoscopically or conventionally. No restriction of age was decided. Patients whose laboratory examinations were not performed (WCC, CRP, or LFTs) did not become the part of the study, participants with liver disease, Gilbert's syndrome, or abnormal LFTs were also extracted through investigation. Positive blood lab examination were those that exceeded the higher limit of the laboratory range<sup>9, 10</sup>.

Thus, hyperbilirubinemia is termed when bilirubin concentration rise above 15 mmol/L. Leukocytosis was termed when WCC concentration increased to  $11 \times 10^9/L$ , and CRP level greater than 10 mg/L were measured high. Patients were categorized into three sub groups based on their appendix histopathology results<sup>9</sup>.

1. The first category (control group) include patients who had a negative appendectomy results histopathologically.
2. The Second sub group involve participants with appendicitis established by histopathology with no perforation.
3. The third category of patients involve appendix with perforation.

## **STATISTICAL ANALYSIS:**

SPSS version 25.0 was used to analyze the data (SPSS, Inc, Chicago, IL). The mean and standard deviation of continuous variables were calculated, as well as the range and median. WCC, CRP, and bilirubin sensitivities, specificities, positive predictive value (PPV), and negative predictive value (NPV) were estimated independently or in groups for participants. The one-way analysis of variance was used to assess the dissimilarity in mean values between the sub groups. When the P value was  $< 0.05$ , the result was considered statistically significant<sup>10</sup>.

## **RESULT:**

	<b>Gender</b>	<b>No Appendicitis%</b>	<b>Appendicitis%</b>	<b>Perforated appendix%</b>
<b>WCC</b>	Males	52.5	79.4	82.3
	Females	40.4	63.2	61.3
<b>CRP</b>	Males	47.3	78.1	92.1
	Females	40.2	73.3	94.3
<b>Bilirubin</b>	Males	26.3	54.3	60.7
	Females	16.6	29.8	50.1

In the appendicitis group, CRP was similar in males and females, respectively, to 78.2 percent and 73.2 percent. The sub category with appendix perforation, CRP was raised by 95 percent of total in most of the participants. Bilirubin is raised in the negative appendicectomy category in 26.3% of men and 16.7% of women. The number is twice for individual with infected appendix (54.4 percent in male, 29.9 percent in females), while it is higher than 60% for subjects with perforated appendicitis<sup>11, 13</sup>.

	WCC	Neutrophil	Lymphocyte	Mono-cyte	AST	ALP	Bili-rubin	CRP
<b>Negative</b>	10.9	8.1	1.9	0.69	23.9	96.8	10.9	32.4
<b>Positive</b>	14.0	11.5	1.5	0.86	26.2	104	17.2	73.3
<b>ANO-VA</b>	P <0.01	P <0.01	P < 0.01	P = 0.02	P = 0.16	P = 0.45	P <0.01	P <0.01

A comparison was made of the White blood count, C reactive protein, bilirubin, aspartate transaminase and alkaline phosphatases among patients with negative appendicectomies and those with confirming appendicitis (single and perforated group appendicitis). The results are summarised in table above. There is a noteworthy differentiation between positive and negative appendicectomy participants in average bilirubin levels 17.2 versus 10.9 where,  $P < .001$ . This dissimilarity is not considerable when compared to the average scores for the other LFTs, such as aspartate transaminase and alkaline phosphatase, indicating isolated hyperbilirubinemia<sup>12</sup>.

	Sensitivity %	Specificity %	Positive predictive value	Negative predictive value
<b>White Cell Count</b>	73.7	55.8	91.4	25.4
<b>C Reactive Protein</b>	76.3	55.6	91.5	27.1
<b>Bilirubin</b>	45.9	80.4	93.2	18.9

	WCC and CRP	CRP and bilirubin	WCC, CRP and bilirubin
<b>Sensitivity in %</b>	57.4	38.5	31.2
<b>Specificity in %</b>	73.7	91.7	95.3
<b>Positive Predictive Value</b>	93.1	96.6	97.5
<b>Negative Predictive Value</b>	21.3	18.9	17.5

Sensitivity, specificity, Positive Predictive Value, and Negative Predictive Value values for White cell count, C reactive protein, and bilirubin were determined in isolation. Additionally, these measures were assessed by collaborating diagnostic biomarkers such as WCC and CRP, CRP and bilirubin, and finally, all diagnostic markers (WCC, CRP, and bilirubin). WCC and CRP appear to have comparable sensitivity, specificity, PPV, and NPV in above tables<sup>13</sup>.

## **DISCUSSION:**

Apparent appendicitis can be complicated to diagnose, particularly within females. Diagnostic and management errors can result in appendix damage and ultimately lead to peritonitis. Though advancements in science and technology has dramatically enhanced, none of the serum biomarkers predict acute appendicitis. As a result, acute appendicitis cannot be diagnosed reliably using a single laboratory examination, but can be predicted through a combination of clinical, laboratory, and radiologic examinations. Awareness of the link between hyperbilirubinemia and appendicitis has increased over the last decade. Perhaps this is explained by the emergency department's excessive ordering of "routine" blood tests. As a result, additional research is conducted to ascertain the hypothesis's validity<sup>13, 14</sup>.

Over 60 years ago, jaundice in the setting of appendicitis was defined in the previous studies. Elevated serum bilirubin levels are believed to occur as a result of portal sepsis or empyema, both of which cause liver hepatocyte dysfunction or damage. It is believed that bacteria producing endotoxins or cytokines are responsible for this. Hyperbilirubinemia develops as a result of direct hepatocyte damage, cholestasis, or a combination of the two. Endotoxins from *Escherichia coli* and *Bacteroides fragilis* have been shown to impair physiological bile flow in vivo in sepsis models<sup>14</sup>.

In a rat liver model, bacterial infection was shown to impair hepatocyte microcirculation and cause hepatocyte damage. Furthermore, endotoxins have been shown to cause hemolysis, leading to an additional rise in bilirubin concentrations<sup>15</sup>.

Growing evidence is available that hyperbilirubinemia is linked to appendicitis. Nevertheless, most of the researches focused on importance of high plasma bilirubin levels in the case of "perforated" appendicitis. The clinical signs of appendix perforation are not faint and, while it is beneficial, hyperbilirubinemia could not be used to alter or speed up our management. The resultant consequences were significant in all participants who had appendicitis, not just those who had perforated appendicitis, using a retrospective case-control design. We recognise that some Gilbert syndrome patients may have been included in our study population. However, this is a little amount because Gilbert's syndrome is an exceptional disease that involve very few percent of Western Europe's population. 24th 25th 26th. Therefore, the presence of elevated serum bilirubins in more than 45 percent of our patients with appendicitis would be sufficient to demonstrate the secondary nature of this hyperbilirubinemia<sup>16, 17</sup>.

According to the current literature review published in the Operational Journal of Europe, additional research is required in combination with analytical biomarkers for acute appendicitis, in the determination of WCC, CRP and bilirubin predictive values. We assessed the diagnostic accuracy of blood markers individually and together in our investigation. The sensitivity of these blood markers remained low after the combination of the results, with a sensitivity of 31,1%

when WCC, CRP and bilirubin are combined. This implies that these tests are not especially sensitive but useful for diagnostic aid, as demonstrated by the extremely high specifications<sup>18</sup>.

We have determined a high specificity of 95% and a PPV of about 98% with the combination of WCC, CRP and bilirubin for appendicitis. There is a 98 per cent chance of appendicitis in patients with correct iliac fossa pain and abnormal WCC, CRP or bilirubin<sup>17</sup>.

Numerous studies have been performed to determine the predictive value of hyperbilirubinemia for appendicular perforation. Giordano et al.<sup>24</sup> concluded within a current systematic review that raised bilirubin independently is not a strong interpreter of piercing. According to Khan, 86% of appendicitis and its complications are affected by hyperbilirubinemia<sup>15, 16</sup>. In 2019, Emmanuel et al. depicted that raised bilirubin is an important predictor of simple acute appendicitis, not only of appendicitis. In addition, the authors have found that 88% positive predictive value (PPV) for simple acute appendicitis and a specificity of 91% for increased serum bilirubin. These findings confirm our own findings, which have found approximately equal results (specificity 80.2 percent and PPV 93.6 percent) .

### **LIMITATION:**

We could not recognize the primary histopathology or the finding in patients with normal histology of the appendix, although the retrospective type of the investigation, led us to high inflammatory markers. It is, however, reasonable to speculate that a urological or gynaecological disease could be the origin<sup>17</sup>.

### **CONCLUSION:**

In the end, our research emphasises the value of biomarkers in acute appendicitis identification. In patients with misunderstandings or in women with degree of difference in analysis of gynecologic pathology, this is particularly important. It also underlines the importance of hyperbilirubinemia in appendicitis diagnosis. However, the diagnosis of acute appendicitis is multifactorial and these tests can help the surgeon to take a decision. Patients with high serum bilirubin levels in the context of right iliac fossa pain warrant early surgery<sup>18</sup>.

### **REFERENCES:**

1. Cusheiri A, Grace PA, Darzi A, et al. Disorders of small intestine and vermiform appendix. In: Cuschieri A, Grace PA, Darzi A, et al. Table 5 Sensitivity, specificity, PPV, and NPV after combining results of WCC and CRP, CRP and bilirubin, and WCC, CRP, and bilirubin WCC 1 CRP 1 bilirubin WCC 1 CRP 1 bilirubin Sensitivity % 57.3 38.3 31.1 Specificity % 73.8 91.8 95.1 PPV % 93.2 96.7 97.6 NPV % 21.4 19 17.6 CRP 5 C-reactive protein; NPV 5 negative predictive value; PPV 5 positive predictive value; WCC 5 white cell count. 1046 The American Journal of Surgery, Vol 209, No 6, June 2015 editors. Clinical Surgery. 2nd ed. UK: Blackwell Publishing Ltd; 2003. p. 405.
2. Paterson – Brown Simon. Acute appendicitis. In: PatersonGrown Simon, Ellis Brian W, Paterson-Brown Simon, editors. Hamilton Bailey's Emergency Surgery. 13th ed. London: Arnold; 2003. p. 399.
3. Smith PH. The diagnosis of appendicitis. Postgrad Med J 1965;41:2–5.

4. Guidry SP, Poole GV. The anatomy of appendicitis. *Am Surg* 1994;60: 68–71.
5. Khan S. Evaluation of hyperbilirubinemia in acute inflammation of appendix: a prospective study of 45 cases. *Kathmandu Univ Med J (KUMJ)* 2006;4:281–9.
6. Ohle R, O'Reilly F, O'Brien KK, et al. The Alvarado score for predicting acute appendicitis: a systematic review. *BMC Med* 2011;9:139.
7. Lintula H, Kokki H, Pulkkinen J, et al. Diagnostic score in acute appendicitis. Validation of a diagnostic score (Lintula score) for adults with suspected appendicitis. *Langenbecks Arch Surg* 2010;395:495–500.
8. Chong CF, Adi MI, Thien A, et al. Development of the RIPASA score: a new appendicitis scoring system for the diagnosis of acute appendicitis. *Singapore Med J* 2010;51:220–5.
9. Emmanuel A, Murchan P, Wilson I, et al. The value of hyperbilirubinaemia in the diagnosis of acute appendicitis. *Ann R Coll Surg Engl* 2011;93:213–7.
10. Sand M, Bechara FG, Holland-Letz T, et al. Diagnostic value of hyperbilirubinemia as a predictive factor for appendiceal perforation in acute appendicitis. *Am J Surg* 2009;198:193–8.
11. Ogilvie TA. Acholuric jaundice and appendicitis. *Br J Surg* 1951;38: 529–30.
12. Ka`ser SA, Fankhauser G, Willi N, et al. C-reactive protein is superior to bilirubin for anticipation of perforation in acute appendicitis. *Scand J Gastroenterol* 2010;45:885–92.
13. Estrada JJ, Petrosyan M, Barnhart J, et al. Hyperbilirubinemia in appendicitis: a new predictor of perforation. *J Gastrointest Surg* 2007;11:714–8.
14. Utili R, Abernathy CO, Zimmerman HJ. Cholestatic effects of Escherichia coli endotoxin endotoxin on the isolated perfused rat liver. *Gastroenterology* 1976;70:248–53.
15. Dawes T, Burrows C. Abdominal pain and jaundice: appendiceal perforation an important differential. *Emerg Med Australas* 2007;19:276–8.
16. McGowan DR, Sims HM, Shaikh I, et al. The value of hyperbilirubinaemia in the diagnosis of acute appendicitis. *Ann R Coll Surg Engl* 2011;93:498.
17. Atahan K, U`reyen O, Aslan E, et al. Preoperative diagnostic role of hyperbilirubinaemia as a marker of appendix perforation. *J Int Med Res* 2011;39:609–18.
18. Ermich S, Kantor Z. [Jaundice in the course of acute appendicitis]. *Pol Tyg Lek* 1970;25:1583–4.