



ORIGINAL ARTICLE

Hyperbilirubinemia as a new predictor of appendicular perforation in acute appendicitis.

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ABSTRACT... Objective: To find the diagnostic accuracy of hyperbilirubinemia as a prediction of appendicular perforation in acute appendicitis. **Study Design:** Cross Sectional study. **Setting:** Department of Surgery, Allama Iqbal Medical College/ Jinnah Hospital Lahore. **Period:** March 2019 to March 2020. **Material & Methods:** A total 345 patients meeting selection criteria were included. Serum bilirubin was measured pre-operatively and histopathology of specimen was collected. The data was analyzed using SPSS v 26 and mean \pm SD, frequency and percentages were calculated. **Results:** There were 214(62%) males and 131(38%) females. On histopathology perforated appendicitis was seen in 70(20.3%) and 275(79.7%) cases had non-perforated appendicitis. A total of 77(22.3%) cases had hyperbilirubinemia and 268(77.7%) of the cases had normal bilirubin level. The sensitivity, specificity, PPV, NPV and diagnostic accuracy of hyperbilirubinemia was 90%, 94.91%, 81.82%, 97.39%, 93.91% respectively. **Conclusion:** The diagnostic accuracy of hyperbilirubinemia is high enough to identify early detection of perforated appendicitis. Hence, by early identification and appropriate management techniques, potentially life-threatening complications can be minimized.

Key words: Diagnostic Accuracy, Hyperbilirubinemia, Histology, Appendicular Perforation.

INTRODUCTION

Acute Appendicitis is the most common emergency surgical procedure and is often missed in female due to mimicking nature of signs and symptoms.^{1,2} Any delay or misdiagnosis carries mortality of 0.3% with morbidity of as perforation around 6%.³ Inflammatory markers and CT scan are helping tools but taking an advantage of CT Pelvis in adult females is still a controversy.³

Serum bilirubin, (a tetrapyrrole,) is produced as a result of degradation of various haemo- proteins like haem part of haemoglobin and myoglobin.⁴ This accumulation of bilirubin due to increased production or decreased clearance in patients with acute appendicitis or perforated appendices might play an important role in early diagnosis of this condition and would ultimately help in reducing mortality and morbidity associated with it.^{4,5}

A study by Sand M et al (n=538; 306 females: 232 males) reported statistically significant (p < 0.05) higher value of serum bilirubin (Mean +SD 1.5 \pm 0.9mg/dl; Range 0.4-4.3 mg/dl) in patients with perforated appendices as compared to those with no perforation but histologically proven acute appendicitis. (Mean \pm SD: 0.9 \pm 0.6 mg/dl; Range 0.1-4.3mg/dl).⁵

Hyperbilirubinemia carries higher specificity for appendicular perforation than White blood cells (WBC) but lesser than C-reactive protein (CRP) (86% vs 55% vs 96%) respectively.⁵ A retrospective study by Emmanuel A et al, (n=472) reported hyperbilirubinemia in patients with inflamed vs non inflamed appendices (p< 0.001). They also reported specificity and Positive predictive value PPV of 88%, 91% respectively.⁶ Locally, similar convincing results with higher specificity, sensitivity, and PPV of hyperbilirubinemia was

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reported by Khan S. et al (100%, 82.07% & 100%).⁷

Despite a number of international studies, there is scarce local data available to establish local guidelines. As we are lacking in availability of CT pelvis in the most of public sector hospitals, if total serum bilirubin is being added to routine laboratory tests of suspected cases then unnecessary delay in these cases would ultimately improve outcome in terms of morbidity and mortality.^{7,8}

MATERIAL & METHODS

This prospective cross-sectional study was carried out in Department of Surgery of Allama Iqbal Medical College, Jinnah Hospital Lahore from March 2019 to March 2020. A non-probability consecutive sampling technique used to select a total of 345 cases (CI: 95%). Demographic profiles of all patients including age and gender were noted. Hyperbilirubinemia was defined as bilirubin level more than 1.3 mg/dl. Perforated acute appendicitis was labeled if any break or tear in the appendix due to appendicitis was noted. Histopathology specimens were reported by a single consultant in order to eliminate bias.

Data was collected through paper form questionnaire and SPSS version 26.0 (IBM Corp. Released 2018. IBM SPSS Statistics for Macintosh, Version 26.0. Armonk, NY: IBM Corp) was used for statistical analysis with appropriate test usagewith appropriate statistical tests applied where applicable. Quantitative data like age of patients, duration of pain and BMI was analyzed by using Mean \pm SD and qualitative variables like gender of patients, hyperbilirubinemia, diagnosis of histopathology proven perforated and non-perforated appendicitis were described using frequency and percentages. Diagnosis of perforated and non-perforated appendicitis on histopathology and Hyperbilirubinemia was tabulated as 2 \times 2 table. Then diagnostic accuracy (sensitivity, specificity, predictive values for the positive and negative value and overall accuracy) of Hyperbilirubinemia was calculated taking histopathology as gold standard. Data was stratified by age and gender, duration of pain and BMI (obese vs non-obese) to address effect modifiers. Post stratification diagnostic accuracy

was calculated. Chi-square test, while considering p-value \leq 0.05 as significant, was applied.

SAMPLE SELECTION CRITERIA

Inclusion Criteria

- Patients aged 18-60 years of both gender
- Right iliac fossa (RIF) pain within 7 days and having Alvarado score $>$ 7 and planned for open appendectomy

Exclusion Criteria

- Patients with viral or alcoholic hepatitis or any known liver disease which has caused jaundice
- Confirmed diagnosis of Cholelithiasis, congenital or acquired biliary disease (on available medical record)
- Haemolytic disorder
- Diagnosis of malignancy of the hepatobiliary system (on available medical record)
- Negative appendectomy on histopathology

RESULTS

The mean age of all cases was 40.51 ± 12.32 years with minimum and maximum age as 18 and 60 years (Table-I). A total of 167(48.4%) cases were 18-40 years old and 178(51.6%) cases were 41-60 years old (Table-I). There were 214(62%) male and 131(38%) female cases with male to female ratio (Table-I). The mean duration of pain was 3.66 ± 1.69 days with minimum and maximum duration as 1 and 6 days (Table-I). There were 160(46.4%) cases who had duration of pain in the past 1-3 days and 185(53.6%) cases had pain for 4-6 days (Table-I). The mean BMI was 28.29 ± 4.32 with minimum and maximum BMI as 21 and 35.60 (Table-I).

There were 134(38.8%) obese and 211(61.2%) non-obese cases in this study (Table-I). On histopathology perforated appendicitis was seen in 70(20.3%) and 275(79.7%) cases had non-perforated appendicitis (Table-I). A total of 77(22.3%) cases had hyperbilirubinemia and 268(77.7%) of the cases had normal bilirubin level (Table-II).

There were 63 cases who had perforated

appendicitis and hyperbilirubinemia 261 cases had non-perforated appendicitis and had normal bilirubin levels while there were 14 cases who had non-perforated appendicitis and had hyperbilirubinemia and there were 7 cases who had perforated appendicitis and normal bilirubin levels. There was significant association between histopathological findings and bilirubin level, p -value < 0.001 . The sensitivity, specificity, PPV, NPV and diagnostic accuracy of hyperbilirubinemia was 90%, 94.91%, 81.82%, 97.39%, 93.91% respectively (Table-III).

When data was stratified for age, gender, duration of pain and BMI we found higher diagnostic accuracy and there was significant association between histopathological findings and bilirubin level, p -value < 0.001 in all strata (Table-I-IV).

DISCUSSION

Acute appendicitis is the most common surgical emergency and is very challenging to diagnose accurately. Application of various clinical, hematological, and radiological tests to confirm diagnosis might delay decision to proceed for surgery.^{8,9} Risk of perforation warrants to proceed for appendectomy in order to avoid perforation related morbidity and mortality but has contributed to unnecessary appendectomies as well. None of the method seems specific, and a clinical assessment in addition to tests is supportive.⁹ Impaired excretion of bile due to bacteremia and or endotoxemia is reported in many literature.¹⁰ Complicated appendicitis lead to hyperbilirubinemia might be used as an indicator to diagnose this condition accurately. Several studies have suggested hyperbilirubinemia in perforated appendicitis but is not well supported.^{3,4,10}

Variables		N=350	Mean + SD	Range	Minimum	Maximum
Age (Years)	18-40 years	167(48.4%)	40.51 + 12.32	42.00	18.00	60.00
	41-60 years	178(51.6%)				
Gender	Males	214(62%)				
	Females	131(38%)				
BMI (Kg/m ²)	< 30	211(61.2%)	28.29 + 4.32	14.60	21.00	35.60
	> 30	134(38.8%)				
Duration of pain (days)	1-3 days	160(46.4%)	3.66 + 1.69	5.00	1.00	6.00
	>3 days	185(53.6%)				

Table-I. Descriptive analysis & Demographic details n=345

	Yes	No
Perforated Appendicitis	275(79.7%)	70(20.3%)
Pre-Op Hyperbilirubinemia	77(22.3%)	268(77.7%)

Table-II. Descriptive analysis & Demographic details n=345

Hyper-bilirubinemia	Histopathology		Total	Sensitivity	Specificity	PPV	NPV	DA
	Perforated	Non Perforated						
Yes	63	14	77	90.00%	94.091%	81.82%	97.39%	93.91%
No	7	261	268					
Total	70	275	345					

Table-III. Comparison of Pre-Operative Hyperbilirubinemia and Histopathological findings

Age Groups (Years)	Hyper-bilirubinemia	Histopathology		Chi-Square	Sensitivity	Specificity	PPV	NPV	DA	P-value
		Perforated	Non perforated							
18-40	Yes	34	9	1.004	87.18%	92.97%	79.07%	95.97%	91.62%	$<0.001^{**}$
	No	5	119							
41-60	Yes	29	5	1.346	93.55%	96.60%	85.29%	98.61%	96.07%	$<0.001^{**}$
	No	2	142							

Table-IV. Comparison of hyperbilirubinemia and histopathological findings with respect to age group

In current study, on histopathology perforated appendicitis was seen in 70 (20.3%) and 275 (79.7%) cases had non-perforated appendicitis. A total of 77 (22.3%) cases had hyperbilirubinemia and 268 (77.7%) of the cases had normal bilirubin level (Table-I). The sensitivity, specificity, PPV, NPV and diagnostic accuracy of hyperbilirubinemia was 90%, 94.91%, 81.82%, 97.39%, 93.91% respectively. Similarly, a study reported statistically significantly ($p < 0.05$) hyperbilirubinemia (Mean + (SD): 1.5 ± 0.9 mg/dL; range, 0.4–4.3 mg/dL) in patients with perforated appendices as compared to those without perforation (Mean + SD: 0.9 ± 0.6 mg/dL; range, 0.1–4.3 mg/dL). Specificity of hyperbilirubinemia vs WBC vs CRP in perforated appendices was 0.86 vs 0.55 vs 0.35 respectively; and sensitivity was 0.7 vs 0.81 vs 0.96 respectively for same. They also reported higher probability of perforated appendicitis in patients with clinically appendicitis and hyperbilirubinemia.⁵ Another study in 2013 reported hyperbilirubinemia in 60 (90%) patients out of 67 perforated appendicitis. They reported sensitivity, specificity, PPV, and NPV for hyperbilirubinemia in perforated appendicitis group as 80%, 89%, 93%, and 96% respectively.⁸ In current study the diagnostic accuracy of hyperbilirubinemia was higher than its counter study (Table-III,IV). In 2013, a study reported statistically raised total and direct bilirubin ($p < 0.01$) in acute and gangrenous/perforated appendicitis. They reported raised level of CRP, total bilirubin, and direct bilirubin level as 14 vs 5 vs 36 times respectively for perforated appendicitis patients ($p < 0.01$ vs $p < 0.05$ vs $p < 0.01$ respectively). It strongly suggests hyperbilirubinemia as an important predictor of perforated appendicitis with low sensitivity (0.38-0.77) but high specificity (0.70-0.87).¹¹ A random effect model with systemic review of eight studies comprising 4974 patients reported hyperbilirubinemia (cutoff 1.0mg/dl) as predictor of perforation carries sensitivity, specificity, positive & negative likelihood, and diagnostic odd ratio as 0.49, 0.82, 2.51, 0.58 & 4.42 respectively. In SROC analysis (with 73% area under curve), hyperbilirubinemia doesn't only accurately diagnose perforated appendicitis but have also rightly predicted perforation; and suggested early appendectomy.¹² Another study

showed similar results supporting our results by indicating relation between hyperbilirubinemia and appendicitis. Hyperbilirubinemia was significantly associated with appendicitis vs RIF pain of other etiologies ($p < 0.0001$). Bilirubin had a higher specificity (0.96), than WBC (0.71) and CRP (0.62), but a lower sensitivity (0.27 vs 0.68 and 0.82 respectively). Hyperbilirubinemia was associated with perforated appendicitis vs simple appendicitis with statistical significance ($p < 0.0001$). Bilirubin had a higher specificity (0.82) than both WBC (0.34) and CRP (0.21), but a lower sensitivity (0.70 vs 0.80 and 0.95 respectively). Hence, the findings confirmed that hyperbilirubinemia has a high specificity for distinguishing acute appendicitis, especially when perforated, from other causes of RIF pain, particularly those not requiring surgery.¹³

A study showed a strong relation between hyperbilirubinemia and perforated appendicitis for pain in RIF among various reasons ($p < 0.001$). They reported that hyperbilirubinemia carries higher specificity (0.96) than both for WBC and CRP (0.34 & 0.21 respectively); but lower sensitivity (0.27) for hyperbilirubinemia than WBC and CRP (0.68 & 0.82 respectively). In perforated appendicitis, they reported again higher specificity and lower sensitivity (0.82 vs 0.70) for hyperbilirubinemia as compared to WBC and CRP (0.34 vs 0.80 & 0.21 vs 0.95) respectively.¹³ A multivariate analysis in 2012 suggested total bilirubin carries statistically significant diagnostic value (OR: 1.772, $p < 0.001$); and significant SIRS score (OR: 1.583; $p < 0.001$) for perforated appendicitis.¹⁴

A recent study (2021) reported sensitivity and specificity of total bilirubin in predicting complicated appendicitis as 91.43% & 88.00% respectively. They reported positive predictive value and negative predictive value were 78.03% and 95.65% respectively.¹⁵ Our study reports significant association between histopathological findings and bilirubin level with p -value < 0.001 . We report sensitivity, specificity, PPV, NPV and diagnostic accuracy of hyperbilirubinemia as 90%, 94.91%, 81.82%, 97.39%, and 93.91% respectively. Irrespective for age, gender, duration

of pain and BMI, we found higher diagnostic accuracy and there was significant association between histopathological findings and bilirubin level, p-value < 0.001 in all groups. Current study has few limitations. This study was conducted in a single institute and did not highlight the role of other laboratory investigations that can predict appendicular perforation. Therefore, we recommend a large multicenter trial to analyze efficacy of combined PPV of bilirubin, CRP, and WBC as a more effective tool.

CONCLUSION

This diagnostic accuracy of hyperbilirubinemia is high enough to utilize in future to get early detection of perforated appendicitis. So, hyperbilirubinemia can help us to predict appendicular perforation in acute appendicitis, by early identification appropriate management techniques can reduce the related risk and potentially life-threatening complications can be minimized.

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2	Sajid Malik	Collection and analysis of data, Manuscript writing.	
3	Muhammad Irfan Zia	Conception and design Provision of study material.	
4	Fatima Tu Zahara	Conception and design Provision of study material.	
5	M. Tauqeer Aslam	Collection and analysis of data, Manuscript writing.	