

ORIGINAL RESEARCH

Prospective Analysis Of Pre-Operative Role Of Rise In Bilirubin In Acute Appendicitis

¹Dr. Ritesh Kumar Agarwal, ²Dr. Jagdish Mutreja, ³Dr. Shashank Rai, ⁴Dr. Anshul Sharma

¹Assistant Professor, ²Associate Professor, Department of General Surgery, School of Medical Sciences & Research (SMS&R), Greater Noida, India

³Assistant Professor, Department of General Surgery, Noida International Institute of Medical Sciences (NIIMS), Greater Noida, India

⁴Senior Resident, ESI Hospital, Okhla, New Delhi, India

Correspondence:

Dr. Anshul Sharma, Senior Resident, ESI Hospital, Okhla, New Delhi, India

Email: sharma17anshul@gmail.com

Received: 12 September, 2022

Accepted: 14 October, 2022

ABSTRACT:

Aim: To study the diagnostic role of rise in bilirubin in Acute appendicitis.

Materials and method: Prospective analytical study of Pre-operative Role of Rise in Bilirubin in acute appendicitis was carried out in December 2019 – April 2021. All cases coming with uncomplicated acute appendicitis admitted during study period in Sharda Hospital, Gr. Noida, UP. were included in study. Patients with Pre-operative diagnosed case of acute appendicitis with age above 18 years were included. The patients with Complicated appendicitis, Negative proved specimen on Histopathology Examination, Patients suffering from Positive HBs Ag, Previous history of Jaundice, Chronic Alcoholism (daily intake of >40 ml for male & >20 ml for female), Patients suffering from Hemolytic Disease, Congenital biliary disease, Hepato-biliary malignancy, Recent history of liver trauma, Cholelithiasis, Females with history of oral contraceptive pill, Patients with history of Statins, Pregnancy were excluded from the study. A detailed history, complete physical examination and routine & appropriate investigations were done for all patients.

Results: The mean age of the study population was 29.46±9.81 (18-70) years with majority of the study population belonging to 18-30 years (62.7%) followed by 31-40 years (22.7%) and above 39 years (14.5%). The study population consisted of 78 (70.9%) males and 32 (29.1%) females. The mean Total Sr. Bilirubin (mg/dL), Direct (mg/dL) and Indirect (mg/dL) among study population was 0.98±0.37 (0.29-2.11), 0.77±0.33 (0.28-1.72) and 0.20±0.21 (0.00-1.73). The mean Alvarado Score of the study population was 7.40±0.59 (7-9). The mean Total Sr. Bilirubin (mg/dL) was significantly more among subjects with Alvarado score ≥ 7 compared to subjects with Alvarado score < 7. Frequency Percent Paracaecal 18 16.4% Pelvic 1 0.9% Retrocaecal 89 80.9% Subcaecal 2 1.8% Total 110 100.0% The Pre-operative findings showed that appendicitis was Paracaecal, among 18 (16.4%), Pelvic, among 1 (0.9%), Retrocaecal, among 89 (80.9%) and Subcaecal, among 2 (1.8%) subjects. There was no significant difference in mean TLC (/mm³) between subjects with Abnormal and Normal

Bilirubin level. The mean C-Reactive Protein (mg/dL) was significantly more among subjects with Abnormal Bilirubin level compared to Normal Bilirubin level.

Conclusion: If bilirubin level is included with Total leucocyte counts, C-reactive protein & ultrasonography, the accuracy of diagnosis can be achieved 100% which had been proven by Histopathological examination, So measuring the Bilirubin level in case of Right iliac fossa pain with probable diagnosis of acute appendicitis has an edge over the accuracy.

Keywords: acute appendicitis, bilirubin, C-Reactive Protein,

INTRODUCTION

There are a numerous causes of pain in the right iliac fossa, but acute appendicitis accounts for about 75% cases, coming as acute surgical emergency in any hospital[1]. Appendicitis is the most common cause of an acute surgical abdomen in all age groups.[2,3] Between 7-10 % of the general population will develop acute appendicitis during their lifetime with the highest incidence being in the second and third decades of life[4-6]. Earlier the diagnosis of acute appendicitis was based on clinical features and physical examinations like tenderness on Mc Burney's point, Rovsing's Sign, Cope's test supported by Total leukocyte counts. With the advancement of ultrasonography[2] and computerized tomography (CT) the diagnosis is now dependent on it. [7]

The accuracy of ultrasound is observer based, while CT is costly and time consuming and diagnosis of Appendicitis still remains a dilemma in spite of advances in radiological and lab investigations.[8,9] Clearly accurate diagnosis is important; to not only prevent misdiagnosis and unnecessary surgery but also to differentiate simple acute appendicitis from a perforated or gangrenous appendix. Emergency surgery is still the treatment of choice for complicated (gangrenous/perforated) appendicitis due to the higher rate of co-morbidity and complications and the need to control the source of sepsis. It is therefore important to stratify patients into those 2 with simple appendicitis who can undergo surgery at a safe opportunity and those with complicated appendicitis that require surgery more urgently.[10]

Several diagnostic scoring systems such as the Alvarado score (Scale 0–10), modified Alvarado score, Paediatric Appendicitis Score (PAS; scale 0–10), Rajalsteri Pengiran Anak Saleha Appendicitis (RIPASA) score for use in Asian patients (Scale 0–14), and Appendicitis Inflammatory Response Score (AIRS; scale 0–12) are commonly used in clinically suspected cases.[11-14] But these scoring systems do not assess the risk of complications like appendicular gangrene or perforation. None of the above mentioned scores use hyperbilirubinemia as a marker. Some studies had showed that risk of appendicular perforation increases three times in subjects with total serum bilirubin levels more than 1 mg/dl.[15] Inflammatory markers are commonly used in the assessment of suspected appendicitis, alongside bilirubin, with these results often influencing the diagnosis.[16,17] Recently some literatures have reported the role of serum bilirubin in the diagnosis of acute appendicitis but importance of raised total bilirubin has not been stressed in acute appendicitis.

Some studies have suggested that bilirubin is only significantly raised when appendiceal perforation takes place,[18,19] this is explored in more detail in a study by *Sand et al.*[20] involving 538 patients; high levels of bilirubin had a specificity of 86 % in perforated appendicitis. As well as perforated appendicitis bilirubin can also be used in the assessment of non-perforated appendicitis and is a specific marker with a positive predictive value of 91.0% according to a recent study by *Emmanuel et al.*[20] The latter is 4 in agreement with a second study by *Ghimire et al.*[21] who report that bilirubin should not be used to predict perforation in appendicitis. Two prospective studies have equivocal[37] and positive results.[23] Overall, it has been suggested that hyperbilirubinaemia might be a better

predictive marker for the perforated appendicitis than white blood cell (WBC) or C-reactive protein (CRP) levels. Some research has also suggested an association between hyperbilirubinaemia and simple appendicitis.[24] The present study was designated to find out the significance of rise in bilirubin as pre-operative diagnostic indicator of clinically diagnosed acute appendicitis and to evaluate its credibility as a diagnostic marker for acute appendicitis pre-operatively.

AIMS AND OBJECTIVES

AIMS

To study the diagnostic role of rise in bilirubin in Acute appendicitis.

PRIMARY OBJECTIVE

To find out the relation between raised Serum bilirubin and acute appendicitis.

SECONDARY OBJECTIVES

- To find out level of bilirubin in uncomplicated appendicitis.
- To find out the significance of raised bilirubin and C-Reactive Protein in the diagnosis of acute appendicitis.
- To find out the relationship between Alvarado's score and levels of bilirubin.

MATERIAL & METHODS

Prospective analysis of Pre-operative Role of Rise in Bilirubin in acute appendicitis.

STUDY DESIGN: Prospective Cross-sectional Analytical Study

STUDY DURATION: December 2019 – April 2021

SAMPLE SIZE: All cases coming with uncomplicated acute appendicitis admitted during study period in Sharda Hospital, Gr. Noida, UP.

STUDY AREA: General Surgery Department in Sharda Hospital, SMSR& H, GR NOIDA.

INCLUSION CRITERIA: Patients with Pre-operative diagnosed case of acute appendicitis with age above 18 years were included

EXCLUSION CRITERIA: The patients with following conditions were excluded from the study: Complicated appendicitis, Negative proved specimen on Histopathology Examination, Patients suffering from Positive HBs Ag, Previous history of Jaundice, Chronic Alcoholism (daily intake of >40 ml for male & >20 ml for female), Patients suffering from Hemolytic Disease, Congenital biliary disease, Hepato-biliary malignancy, Recent history of liver trauma, Cholelithiasis, Females with history of oral contraceptive pill, Patients with history of Statins, Pregnancy.

STUDY PROCEDURE

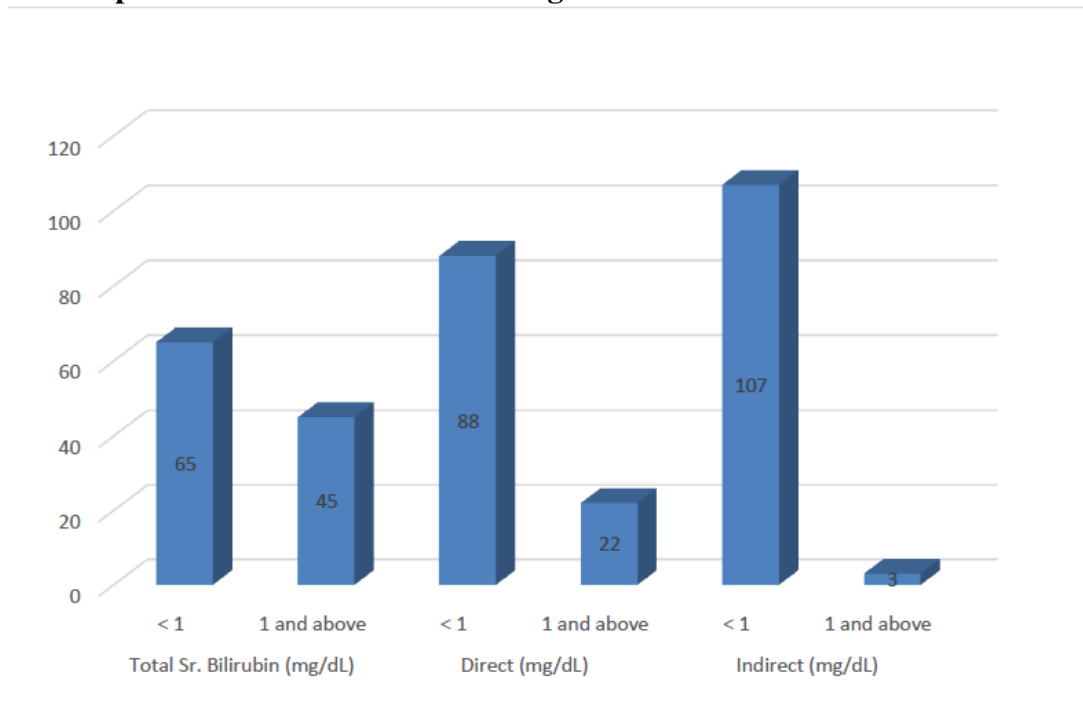
It was conducted after clearance from Board of Studies and Ethical committee in the Department of General Surgery, Sharda Hospital, SMSR& Hospital, Greater Noida. All patients were selected as per inclusion and exclusion criteria. A detailed history, complete physical examination and routine & appropriate investigations were done for all patients.

STATISTICAL ANALYSIS

The data was entered into the Microsoft excel and the statistical analysis was performed by statistical software SPSS version 25.0. The Quantitative (Numerical variables) were present in the form of mean and SD and the Qualitative (Categorical variables) were present in the form of frequency and percentage. The student t-test was used for comparing the mean values between the 2 groups whereas chi square test was applied for comparing the frequency. The p-value was considered to be significant when less than 0.05.

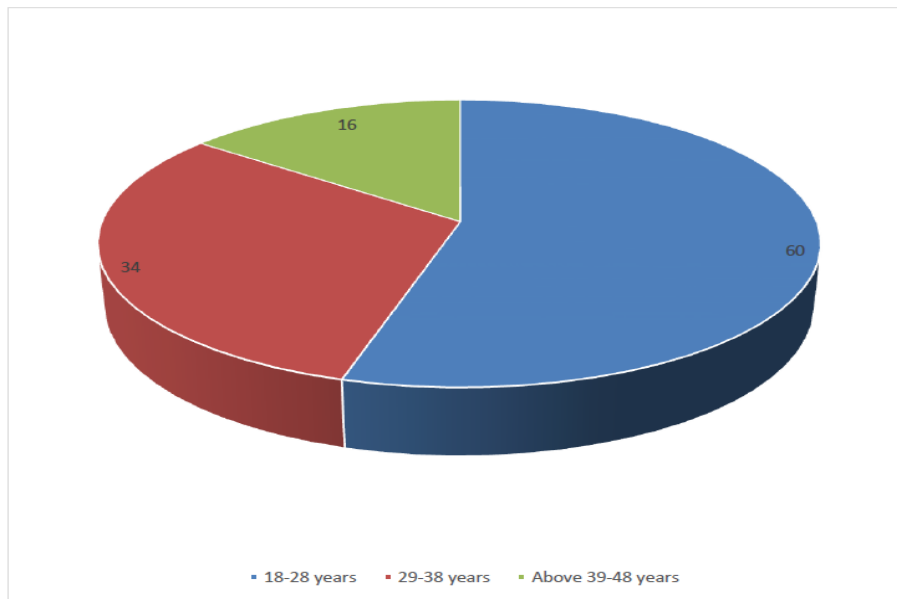
RESULTS

Fig. 1: total patients with raised bilirubin > 1g/dl



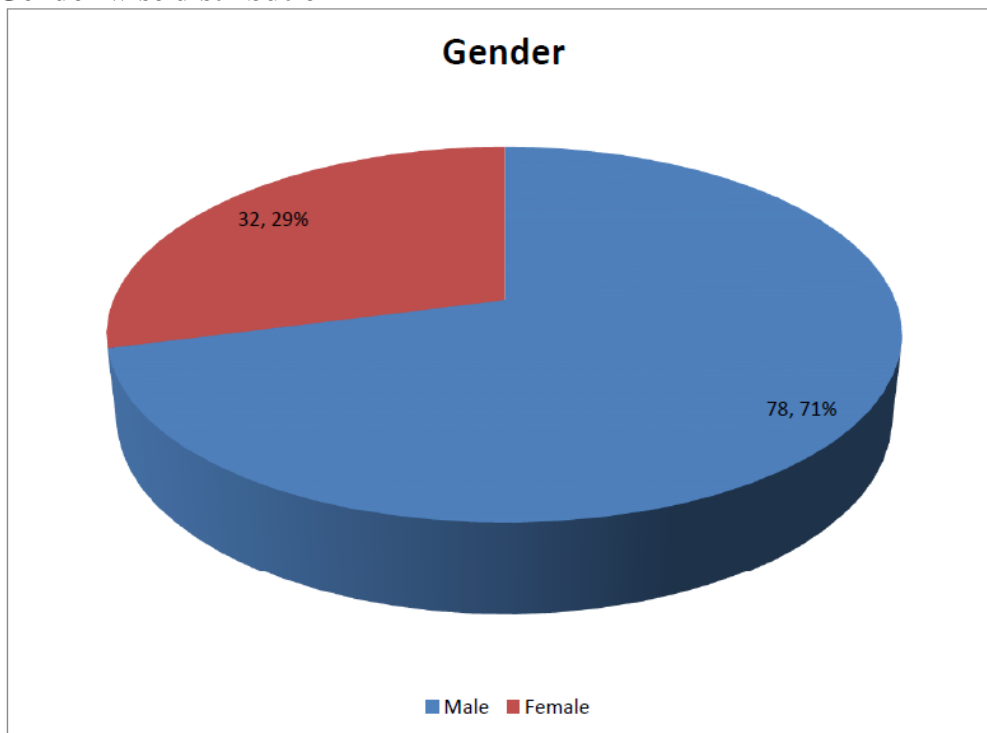
The mean age of the study population was 29.46 ± 9.81 (18-70) years with majority of the study population belonging to 18-30 years (62.7%) followed by 31-40 years (22.7%) and above 39 years (14.5%).

Fig. 2: Showing Age wise distribution



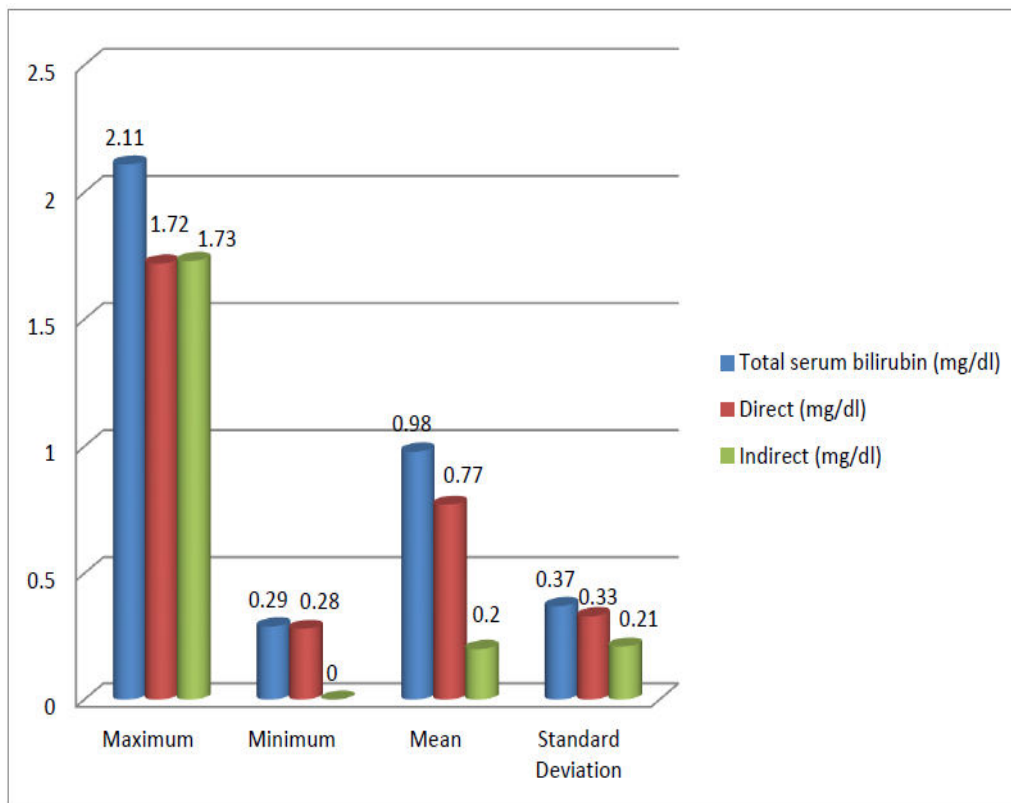
The study population consisted of 78 (70.9%) males and 32 (29.1%) females.

Fig. 3: Gender wise distribution



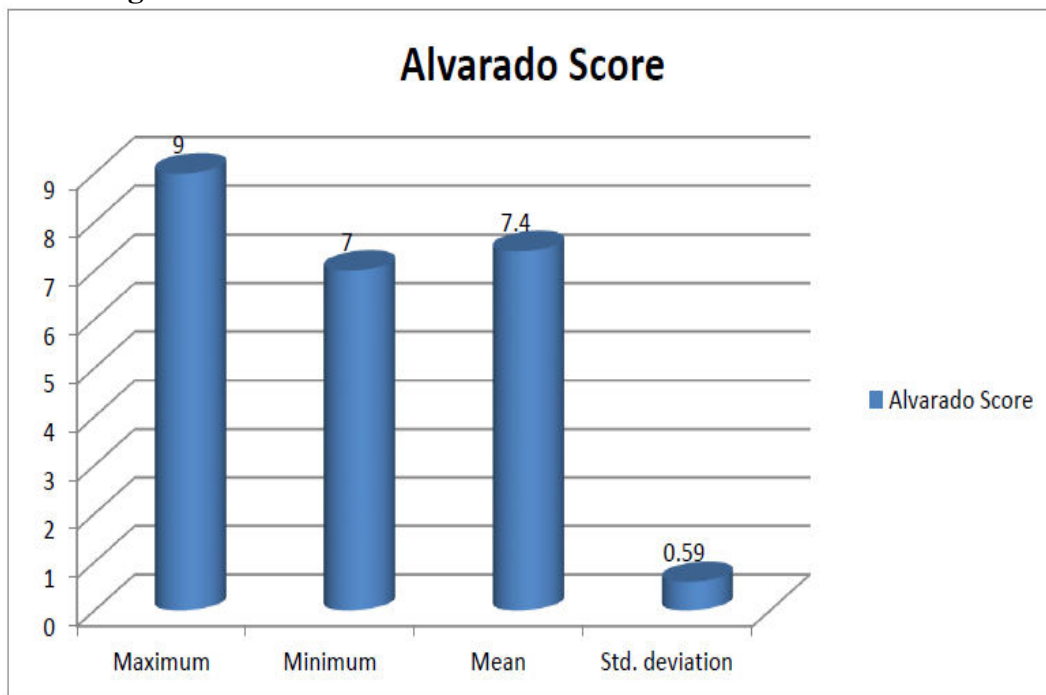
The mean Total Sr. Bilirubin (mg/dL), Direct (mg/dL) and Indirect (mg/dL) among study population was 0.98 ± 0.37 (0.29-2.11), 0.77 ± 0.33 (0.28-1.72) and 0.20 ± 0.21 (0.00-1.73).

Fig. 4: Showing mean & Std Deviation of patients with increased bilirubin



The mean Alvarado Score of the study population was 7.40 ± 0.59 (7-9).

Fig. 5: Showing mean & Std Deviation of Alvarado score



The mean Total Sr. Bilirubin (mg/dL) was significantly more among subjects with Alvarado score ≥ 7 compared to subjects with Alvarado score < 7 .

Fig. 6: showing mean serum bilirubin in Alvarado score > 7

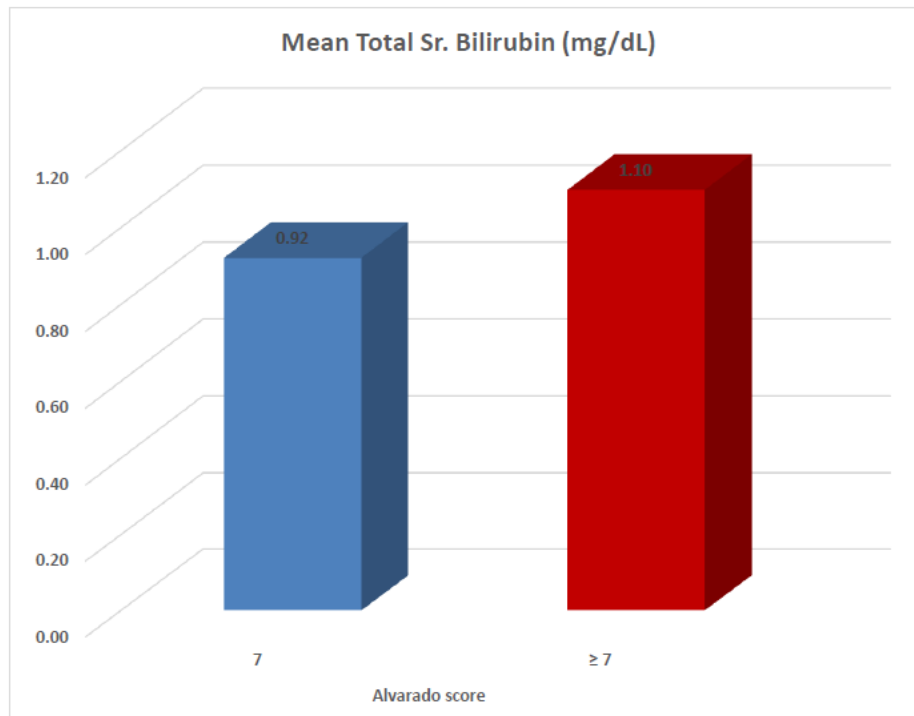


Table 1: showing positions of appendix: Per-operative finding

Per-operative finding	Frequency	Percent
Paracaecal	18	16.4%
Pelvic	1	0.9%
Retrocaecal	89	80.9%
Subcaecal	2	1.8%
Total	110	100.0%

Frequency Percent Paracaecal 18 16.4% Pelvic 1 0.9% Retrocaecal 89 80.9% Subcaecal 2 1.8% Total 110 100.0% The Pre-operative findings showed that appendicitis was Paracaecal, among 18 (16.4%), Pelvic, among 1 (0.9%), Retrocaecal, among 89 (80.9%) and Subcaecal, among 2 (1.8%) subjects.

Table 2 showing USG reports range USG

USG	Frequency	Percent
Acute Appendicitis	110	100.0%
Total	110	100.0%

USG showed that all (100.0%) subjects had acute appendicitis.

Table 3: Table showing mean & std deviation of increased bilirubin using unpaired t-test

Bilirubin	Age				
	Mean	Std. Deviation	Mean Difference	t-test value	p-value
Normal	27.92	7.84	-3.77	-2.252	0.026*
Abnormal	31.69	11.85			

The mean age of the study population was compared between subjects with Normal and Abnormal Bilirubin level using the unpaired t-test. The mean age of the study population was significantly more among subjects with Abnormal Bilirubin level compared to Normal Bilirubin level.

Table 4: Table showing mean & std deviation of increased TLC with increased bilirubin using unpaired t-test

Bilirubin	TLC (/mm ³)				
	Mean	Std. Deviation	Mean Difference	t-test value	p-value
Normal	15943.62	3027.26	-656.59	-1.341	0.183
Abnormal	16600.20	3754.46			

The mean TLC (/mm³) was compared between subjects with Normal and Abnormal Bilirubin level using the unpaired t-test. There was no significant difference in mean TLC (/mm³) between subjects with Abnormal and Normal Bilirubin level.

Table 5: Table showing mean & std deviation of increased CRP with increased bilirubin using unpaired t-test

Bilirubin	C-Reactive Protein (mg/dL)				
	Mean	Std. Deviation	Mean Difference	t-test value	p-value
Normal	6.26	2.03	-1.58	-2.500	0.037*
Abnormal	7.84	3.89			

The mean C- reactive protein (mg/dL) was compared between subjects with Normal and Abnormal Bilirubin level using the unpaired t-test. The mean C-Reactive Protein (mg/dL) was significantly more among subjects with Abnormal Bilirubin level compared to Normal Bilirubin level.

Table 6: Table showing HPE range with increased bilirubin levels

Bilirubin	HPE report	
	AA	AP
Normal	65	0
	60.2%	.0%
Abnormal	43	2
	39.8%	100.0%
□2 value = 2.942, p-value = 0.046*		

Table 7: Table showing Alvarado score with increased bilirubin using unpaired t-test

Bilirubin	HPE report	
	AA	AP
Normal	65	0
	60.2%	.0%
Abnormal	43	2
	39.8%	100.0%
□2 value = 2.942, p-value = 0.046*		

DISCUSSION

A biological marker or biomarker can be defined as an objectively, measurable characteristic that previous research has validated as a marker of a normal physiology, disease or the disease's response to treatment.[10] The diagnostic value of laboratory investigations has been established in patients with appendicitis.[25,26] Laboratory tests chosen to aid in the

diagnosis of appendicitis are based on their availability, low costs, minimally invasive nature and repeatability.[26] Bilirubin is felt to rise as a response to intra-abdominal infection causing transiently portal pyrexia and resulting inflammatory-mediated cholestasis.[21] Our results show that serum bilirubin measured on admission could be useful in determining the diagnosis of appendicitis. The results corroborate the use of bilirubin as a marker of inflammation or gangrene/perforation when in combination with other inflammatory markers such as CRP and WBC as it has been shown to have good true positive rate. However, we cannot suggest that bilirubin be used as a marker of gangrene/perforation or be used as an independent marker in its own right. **Age** In our study, the mean age of the study population was 29.46 ± 9.81 (18-70) years with majority in the age group of 18-30 years (62.7%) followed by 31-40 years (22.7%) and above 40 years (14.5%). Similar to our study, Emmanuel et al.[20] found that mean age was 27 years (range: 5–82 years) and *D'souza et al.* [27] found that the age ranged from 18 to 89 years (mean = 33.6 years). **Gender** The study population consisted of 78 (70.9%) males and 32 (29.1%) females. *Emmanuel et al.*[20] found that 53.8% were male. *Patel et al.*[28] found that 71% were males while the remaining 29% were females **Bilirubin** The mean Total Sr. Bilirubin (mg/dL), Direct (mg/dL) and Indirect (mg/dL) among study population was 0.98 ± 0.37 (0.29-2.11), 0.77 ± 0.33 (0.28-1.72) and 0.20 ± 0.21 (0.00-1.73). The total bilirubin was found to be abnormal among 40.9% subjects. The mean Total Sr. Bilirubin (mg/dL) among subjects with acute appendicitis was 0.97 ± 0.37 and acute perforative appendicitis was 1.13 ± 0.25 . In contrast to our study, *Patel et al.*[28] found that Hyperbilirubinemia (> 1.0 mg/dL) in our study was found in 82% patients, while 18% had normal bilirubin levels (≤ 1.0 mg/dL) range, (0.85– 1.75 mg/dL), which was above the normal range (≤ 1.0 mg/dL) considered for the study, hence indicating the occurrence of hyperbilirubinemia. 65.33% patients diagnosed with Acute uncomplicated appendicitis were found to have elevated bilirubin levels (> 1.0 mg/dL) while 34.67% patients had normal bilirubin levels (≤ 1.0 mg/dL). *Adams et al.*[29] stated that Serum bilirubin, despite being within its normal range was significantly higher in cases of appendicitis compared with cases demonstrating a histologically normal appendix. Hyperbilirubinemia has previously been reported as a predictive factor of appendicitis. *Svincet al.*[30] reported that hyperbilirubinemia (>1.0 mg/dL) and high neutrophil-to-lymphocyte ratio (>4.8) were significantly associated with perforated appendicitis among 3392 cases (odds ratios 2.6 and 2.6, respectively). *Erenet al.*[31] found that high CRP (>0.5 mg/dL) and hyperbilirubinemia (>1.2 mg/dL) were associated with gangrenous or perforated appendicitis. *56 Nomura et al.*[32] identified hyperbilirubinemia as a risk factor for gangrenous appendicitis among 410 patients (odds ratio 1.7919). There have been several reports of hyperbilirubinaemia in appendicitis.[33,34] *Estrada et al.*[25] hypothesised that hyperbilirubinaemia may be associated with appendiceal perforation and showed that more patients with a perforated or gangrenous appendix had hyperbilirubinaemia than those with simple acute appendicitis. *Sandet al.*[35] showed that the specificity of serum bilirubin was higher (86%) than other markers like WBC (55%) and C-reactive protein (CRP) (35%) in diagnosing gangrenous and perforated appendicitis.

CRP marker In our study, majority of the study had C - reactive protein value 5-10 mg/dl (81.8%) followed by < 5 mg/dl (12.7%) and > 10 mg/dl (5.5%). The mean C- reactive protein (mg/dL) level among study population was 6.90 ± 3.02 (1.60-29.00). *Motie et al.*[36] found that CRP levels had a significant difference between the different pathological groups. A study conducted by *Beltran et al.* showed a high sensitivity and low specificity for CRP to predict perforated appendicitis. They also concluded that CRP performed better than any other inflammatory marker, laboratory test, clinical variable, or SIRS to predict perforated appendicitis.[37] These results were repeated by *Panagiotopoulou et al.* and *Käseret*

al.[38,39] In Anderson's study, inflammatory markers including CRP was as strong as clinical symptoms to predict advanced appendicitis.[31] A retrospective study by *Sandet al.*,[35] involving 538 patients, investigated the value of blood bilirubin levels in the diagnosis of acute suppurative or perforated appendicitis. That study found the specificity of high bilirubin levels to be 86% for the diagnosis of perforated appendicitis.

Histopathological examination (HPE) HPE report showed that 98.2% subjects had acute appendicitis and 1.8% subjects had acute perforative appendicitis. *D'souza et al.*[40] in their study showed that histology revealed simple appendicitis in 63% cases, and perforated appendicitis in 14% cases. The cases of simple appendicitis included acute, gangrenous and resolving appendicitis. Patel et al.[28] stated that histopathologically, 75% patients were confirmed as Acute Uncomplicated appendicitis while 25% were diagnosed as complicated appendicitis.

Alvarado score The Alvarado score is a clinical scoring system used in the diagnosis of appendicitis[41] The score has 6 clinical items and 2 laboratory measurements with a total 10 points. A score of 5 or 6 is compatible with the diagnosis of acute appendicitis. A score of 7 or 8 indicates a probable appendicitis, and a score of 9 or 10 indicates a very probable acute appendicitis.[42] In current study, Alvarado Score 8 and 9 was significantly more among subjects with Abnormal Bilirubin levels. Ghimire et al.[21] found that the effect size as indicated by eta square statistics was small for total Alvarado's score and total count (eta square = 0.09 and 0.05 respectively) and large for total bilirubin (eta squared=0.39). 59

Ultrasonography (USG) USG showed that all (100.0%) subjects had acute appendicitis. The diagnostic utility of ultrasonography for acute appendicitis has been emphasized and widely accepted, especially for the paediatric and pregnant patient groups.[43] No single clinical or laboratory investigation has been demonstrated to reliably predict appendicitis. Instead, a combination of history, examination, laboratory and radiological investigations are recommended to determine the most likely diagnosis and management.[20] Hyperbilirubinaemia has been inadequately investigated as a potential laboratory indicator for the preoperative diagnosis of perforated appendicitis. Both increased bilirubin production and alterations in bilirubin clearance can lead to bilirubin accumulation and may be involved in the hyperbilirubinaemia observed in patients with appendix perforation.[44] So, it can be inferred that the patients with features suggestive of appendicitis with higher values of bilirubin, are more susceptible of having complicated appendicitis than those with normal or slightly elevated total serum bilirubin. The diagnosis of appendicitis is still based on a patient's clinical presentation, and the judgement of the emergency surgeon. The most common investigative adjuncts are blood tests,urinalysis and imaging. As appendicectomy is carried out routinely during these operations, there has been a concurrent increase in the negative appendicectomy rate in some trusts. A correct pre-operative diagnosis could reduce the number of possibly unnecessary operations with the costs of theatre time, hospital stay and time off work to recover, as well as the risks of complications.[40]

LIMITATIONS

It is a retrospective. Not all patients who underwent an emergency appendicectomy had pre-operative bilirubin levels collected; this led to a smaller sample population due to exclusion criteria.

We recommend that a prospective study should be completed to employ a sufficient study population and the collection of pre-operative bilirubin samples.

SUMMARY

In our study minimum age suffering from acute appendicitis was 18 yrs & maximum age was 70 yrs leading to mean age of 29.46 ± 9.81 .

The study population consisted of 78 (70.9%) males and 32 (29.1%) females.

The mean Total Sr. Bilirubin (mg/dL), Direct (mg/dL) and Indirect (mg/dL) among study population was 0.98 ± 0.37 (0.29-2.11), 0.77 ± 0.33 (0.28-1.72) and 0.20 ± 0.21 (0.00-1.73) respectively.

The mean C-reactive protein (mg/dL) level among study population was 6.90 ± 3.02 (1.60-29.00). The mean duration of hospital stay among study population was 2.84 ± 0.55 (2.00-4.00).

Ultrasonography had shown 100% accuracy in this study.

All the Histopathologically proven appendicitis patients per-operatively showed Retrocaecal 89 (80.9%), Paracaecal 18 (16.4%), Subcaecal 2 (1.8%), Pelvic 1 (0.9%).

Histopathological Examination report showed that 108 (98.2%) subjects had acute appendicitis.

Conclusion

To conclude in this study, if bilirubin level is included with Total leucocyte counts, C-reactive protein & ultrasonography, the accuracy of diagnosis can be achieved 100% which had been proven by Histopathological examination, So measuring the Bilirubin level in case of Right iliac fossa pain with probable diagnosis of acute appendicitis has an edge over the accuracy.

BIBLIOGRAPHY

1. Ditillo MF, Dziura JD, Rabinovici R. Is it safe to delay appendectomy in adults with acute appendicitis? *Ann Surg* 2006;244:656-60.
2. Ozguner IF, Buyukayavuz BI, Savas MC. The influence of delay on perforation in childhood appendicitis. A retrospective analysis of 58 cases. *Saudi Med J*. 2004;25:1232-6.
3. Zhang Y, Zhao YY, Qiao J. Diagnosis of appendicitis during pregnancy and peritoneal outcome in the late pregnancy. *Chin Med J*. 2009;122:521-4.
4. Khalil J, Muqim R, Rafique M, Khan M. Laparoscopic versus open appendectomy: a comparison of primary outcome measures. *Saudi J Gastroenterol*. 2011;17(4):236-40.
5. Fahim F, Shirjeel S. A comparison between presentation time and delay in surgery in simple and advanced appendicitis. *J Ayub Med Coll Abbottabad*. 2005;17:37-9.
6. Kumar B, Samad A, Khanzada TA, Shaikh AR. Superiority of laparoscopic appendectomy over open appendectomy: the Hyderabad experience. *Rawal Med J*. 2008;33:165-8.
7. Mostbeck G, Adam EJ, Nielsen MB, Claudon M, Clevert D, Nicolau C, Nyhsen C, Owens CM. How to diagnose acute appendicitis: ultrasound first. *Insights Imaging*. 2016;7(2):255-63.
8. De Castro SM, Unlu C, Steller EP, van Wagenveld BA, Vrouwenraets BC. Evaluations of the appendicitis inflammatory response score for patients with acute appendicitis. *World J Surg*. 2012;36:1540-5.
9. Ohle R, O'Reilly F, O'Brien KK, Fahey T, Dimitrov BD. The Alvarado score for predicting acute appendicitis: a systematic review. *BMC Med*. 2011;9:139. 62
10. Chambers AC, Bismohun SL, Davies H, White P, Patil AV. Predictive value of abnormally raised serum bilirubin in acute appendicitis: a cohort study. *Int J Surg*. 2015;13:207-10.

11. Pickhardt PJ, Lawrence EM, Pooler BD, Bruce RJ. Diagnostic performance of multidetector computed tomography for suspected acute appendicitis. *Ann Intern Med.* 2011;154:789–96.
12. Kalan M, Talbot D, Cunliffe WJ, Rich AJ. Evaluation of the modified Alvarado score in the diagnosis of acute appendicitis: a prospective study. *Ann R Coll Surg Engl.* 1994;76:418–9.
13. Escriba A, Gamell AM, Fernandez Y, Quintillá JM, Cubells CL. Prospective validation of two systems of classification for the diagnosis of acute appendicitis. *Pediatr Emerg Care.* 2011;27:165–9.
14. Chong CF, Thien A, Mackie AJ, Tin AS, Tripathi S, Ahmad MA. Comparison of RIPASA and Alvarado scores for the diagnosis of acute appendicitis. *Singapore Med J.* 2011;52:340–5.
15. Petroianu A. Diagnosis of acute appendicitis. *Int J Surg.* 2012;10(3):115–9.
16. Khan S. The diagnostic value of hyperbilirubinemia and total leucocyte count in the evaluation of acute appendicitis. *JCDR.* 2009;3:1647–52.
17. De Dombal FT, Leaper DJ, Staniland JR, et al. Computer-aided diagnosis of acute abdominal pain. *BMJ.* 1972;2:9–13.
18. Ortega-Deballon P, Ruiz de Adana-Belbel JC, Hernandez-Matias A, et al. Usefulness of laboratory data in the management of right iliac fossa pain in adults. *Dis Colon Rectum.* 2008;51:1093–9.
19. Gronroos JM, Gronroos P. Leucocyte count and C-reactive protein in the diagnosis of acute appendicitis. *Br J Surg.* 1999;86:501–4.
20. Emmanuel A, Murchan P, Wilson I, Balfe P. The value of hyperbilirubinaemia in the diagnosis of acute appendicitis. *Ann R Coll Surg Engl.* 2011 Apr;93(3):213-7.
21. Ghimire P, Thapa P, Yogi N, Ghimire P. Role of serum bilirubin as a marker of acute gangrenous appendicitis. *NJMS.* 2012;1(2):89–92.
22. Beltran M, Mendez P, Barrera R, Contreras M, Wilson C, Cortes V, et al. Is hyperbilirubinaemia in appendicitis a better predictor of perforation than C-reactive protein? a prospective study. *Indian J Surg* 2009;71(5):265-72.
23. Khan S. Elevated serum bilirubin in acute appendicitis; a new diagnostic tool . *Kathmandu Univ med J (KUMJ).* 2008;6(2): 161-5
24. Emmanuel A, Murchan P, Wilson I, Balfe P. The value of hyperbilirubinaemia in the diagnosis of acute appendicitis. *Ann R Coll Surg Engl* 2011;93(3):213-7.
25. Estrada JJ, Petrosyan M, Barnhart J, et al. Hyperbilirubinemia in appendicitis: a new predictor of perforation. *J Gastrointest Surg.* 2007;11:714–8.
26. Kim E, Subhas G, Mittal VK, et al. C-reactive protein estimation does not improve accuracy in the diagnosis of acute appendicitis in pediatric patients. *Int J Surg.* 2009;7:74– 7.
27. de Souza SC, da Costa SDMR, de Souza IGS. Vermiform appendix: positions and length – a study of 377 cases and literature review. *j coloproctol (rio j).* 2015;35(4):212-6.
28. Patel D, Shah NJ, Patel B, Parikh M, Patel D, Dalal C. Evaluation of hyperbilirubinemia as a new diagnostic marker for acute appendicitis and its role in the prediction of complicated appendicitis. *Int J Res Med.* 2014;3(3):28-33.
29. Adams HL, Jaunoo SS. Hyperbilirubinaemia in appendicitis: the diagnostic value for prediction of appendicitis and appendiceal perforation. *Eur J Trauma Emerg Surg.* 2016;42(2):249-52.
30. Sevinç MM, Kınacı E, Çakar E, Bayrak S, Özakay A, Aren A, Sarı S. Diagnostic value of basic laboratory parameters for simple and perforated acute appendicitis: an analysis of 3392 cases. *Ulus Travma Acil Cerrahi Derg.* 2016;22(2):155-62.

31. Andersson RE. Meta-analysis of the clinical and laboratory diagnosis of appendicitis. *Br J Surg.* 2004;91(1):28-37.
32. Nomura S, Watanabe M, Komine O, Shioya T, Toyoda T, Bou H, Shibuya T, Suzuki H, Uchida E. Serum total bilirubin elevation is a predictor of the clinicopathological severity of acute appendicitis. *Surg Today.* 2014;44(6):1104-8.
33. Agrez MV, House AK, Quinlan MF. Jaundice may herald an appendiceal abscess. *Aust N Z J Surg* 1986;56:511-3.
34. Dawes T, Burrows C. Abdominal pain and jaundice: appendiceal perforation an important differential. *Emerg Med Australas.* 2007;19:276–278.
35. 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.
36. Motie MR, Nik MM, Gharaee M. Evaluation of the diagnostic value of serum level of total bilirubin in patients with suspected acute appendicitis. *Electron Physician.* 2017;9(4):4048- 54.
37. Beltran MA, Mendez PE, Barrera RE, Contreras MA, Wilson CS, Cortes VJ, et al. Is hyperbilirubinaemia in appendicitis a better predictor of perforation than C-reactive protein?
38. Panagiotopoulou IG, Parashar D, Lin R, Antonowicz S, Wells AD, Bajwa FM, Krijgsman B. The diagnostic value of white cell count, C-reactive protein and bilirubin in acute appendicitis and its complications. *Ann R Coll Surg Engl.* 2013;95:215-221.
39. Käser SA, Fankhauser G, Willi N, Maurer CA. C-reactive protein is superior to bilirubin for anticipation of perforation in acute appendicitis. *Scand J Gastroenterol.* 2010 Aug;45(7- 8):885-92. 64.
40. D'Souza N, Karim D, Sunthareswaran R. Bilirubin; a diagnostic marker for appendicitis. *Int J Surg.* 2013;11(10):1114-7. 68
41. Alvarado A. A practical score for the early diagnosis of acute appendicitis. *Annals of Emergency Medicine.* 1986;15(5):557-64.
42. Douglas CD, Macpherson NE, Davidson PM, Gani JS. Randomised controlled trial of ultrasonography in diagnosis of acute appendicitis, incorporating the Alvarado score. *BMJ.* 2000;321(7266):919-22.
43. Barloon TJ, Brown BP, Abu-Yousef MM, Warnock N, Berbaum KS: Sonography of acute appendicitis in pregnancy. *Abdom Imaging.* 1995;20:149-151.
44. Atahan K, Üreyen O, Aslan E, Deniz M, Çökmez A, Gür S, Avcı A, Tarcan E. Preoperative diagnostic role of hyperbilirubinaemia as a marker of appendix perforation. *J Int Med Res.* 2011;39(2):609-18.