

SERUM BILIRUBIN RELIABLE DIAGNOSTIC MARKER IN DETECTING COMPLICATED APPENDICITIS

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ABSTRACT

BACKGROUND

The aims of the study were: 1) To establish hyperbilirubinemia as a Reliable marker in gangrenous/perforated appendicitis; and 2) To compare other variables such as white blood cell count and Alvarado score in a similar manner.

METHODS

This is a prospective cohort single centred study done on 100 patients of acute appendicitis admitted to our hospital through emergency and surgical OPD. Clinical examination, laboratory and radiological investigations were done to establish the diagnosis. Alvarado score was performed in every case to assess the severity of the disease pre-operatively. All the post-operative specimens were subjected to histo-pathological examination for confirmation of the diagnosis. The clinical and laboratory data was compiled and analysed. Statistical analysis was performed using SPSS program for Windows version 21.0. P value <0.05 was considered as significant.

RESULTS

Marked raise of Total serum bilirubin was found in Gangrenous and impending perforated appendix. Even though TLC was raised, it was not consistent in all cases of gangrene or perforated appendicitis. The P value of TLC was 0.016 and the P value of total serum bilirubin was 0.000, which is definitely significant.

CONCLUSION

Serum bilirubin is a reliable diagnostic marker in acute appendicitis particularly in gangrenous/perforated appendicitis.

KEYWORDS

Abdominal pain, Acute appendicitis, Appendectomy.

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INTRODUCTION: Acute appendicitis (AA) is most common surgical emergency, associated with high incidence of morbidity and occasional mortality if not attended early. (ICDR, graffito, chetri).^{1,2} Recent studies worldwide also reveal its incidence is more than 8%. (Sauerland S, Lefering R, Neugebauer EAM).³ with its lifetime prevalence accounts for 1 in 7. (Stephens PL and Mazzucco JJ).⁴ Early detection and timely management followed by appropriate treatment modalities will reduce the severity of the appendicitis and its complications. (Reddy GVB, et al.).⁵ We are aware that majority of the cases will be diagnosed clinically by assessing the symptoms and physical signs, further confirmed by laboratory tests (Oruch MT, Taha AS, Hallan S, Goodwin AT, Albu E).^{6,7,8,9,10} and radiological investigations (Douglas CD, Rettenbacher T, Walker S).^{11,12} along with Alvarado score (Alvarado A, Puylaert JB and Pearson RH).^{13,14} However, diagnosis will be difficult sometimes even after performing

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all these tests. In such doubtful cases, misdiagnosis leads to removal of the patient's normal appendix, (Karakas SP, Hoffmann J).^{15,16} which results in increased morbidity. If the diagnosis is delayed, it results in complications like rupture and abscess/peritonitis and their complications including death.

There are many conditions mimicking appendicitis like Meckel's diverticulitis, mesenteric lymphadenitis, Rt. ureteric calculus lower 1/3, ovarian torsion, etc. However, the accurate diagnosis and severity of appendicitis (gangrene/perforation) may be missed sometimes even with the help of scoring systems like Alvarado or radiological imaging like ultrasonography (Douglas CD).¹¹ CT (Hongjj).¹⁷ MRI (Incesu L).¹⁸ Majority of prospective studies reported 22-30% removal of normal appendix with surgery (JCDR).³⁻⁶ Thus accurate diagnosis and timely intervention is necessitated.

Hyperbilirubinemia is noted in septic conditions due to cholestasis. The association between the hyperbilirubinaemia and the variety of infectious diseases has been noted in few studies [Johnson AM, Miller DJ, Whitehead MW]. This finding most commonly occurs in neonates with gram negative bacterial infection. It has also been described in patients with severe intra-abdominal infections. The pathogenesis is thought to be because of

bacteremia or endotoxemia causing impaired excretion of bilirubin from the bile canaliculi.

Bacterial invasion of abdominal organs causes transmigration of bacteria. After reaching to liver parenchyma through superior mesenteric vein they produce inflammation, abscess formation either directly or indirectly by altering the hepatic blood flow. But when bacterial load overwhelms the Kupffer cell function, it may cause dysfunction or damage to hepatocytes (liver parenchyma). It reflects a rise in Serum Bilirubin (SB) alone or in combination with liver enzymes depending upon the type, severity and site of the lesion. Recently, another substance known as cytokines, e.g. interleukin (IL)-6, Tumor Necrosis Factor (TNF) has also been considered to be responsible for depressed excretory function of the liver and may lead to increase in SB levels without a rise in liver enzymes.

Present study was undertaken to confirm the association of hyperbilirubinemia as preoperative marker in appendicitis particularly in gangrenous, impending rupture or perforation. The evaluation of other parameters such as age, duration of symptoms, TLC, Alvarado score was taken in account of all the cases.

MATERIAL AND METHODS:

Study Design: A single centred, prospective and cohort study, conducted on 100 consecutive patients. The diagnosis of acute appendicitis was made clinically in emergency and surgical OPD and were admitted to General Surgery Ward of Narayana Medical College and Hospital, Nellore.

Period of Study: The work was carried out during the period of July 2011 to May 2014.

Inclusion Criteria: Patients of any age group and of both sexes presenting to Surgery department with symptoms of acute appendicitis with informed consent were included.

Exclusion Criteria: 1) Patients presenting with urological, gynaecological or other surgical problems. 2) In those where serum bilirubin is raised due to any cause other than appendicitis, 3) Those who are not willing/interested were excluded from this study.

The admitted patients were subjected to detailed history and routine clinical examination. Investigations were done immediately, which included TC, DC, Ultrasonography of abdomen and total serum bilirubin and other baseline investigations like Hb, Blood sugar, RFT, Blood group and routine urine examination, X-ray chest, X-ray KUB and ECG to rule out any pathology.

A Proforma containing general information about the patient was filled taking in to consideration of Alvarado scoring system also. A score up to 4 was treated conservatively. Patient with a score of 5 was observed for 1 day and was subjected to appendectomy, as there was no improvement conservatively. Patient with a score of 6 and above were immediately taken up for surgery. All the cases who underwent surgery, the specimen was sent to

histopathology and compared with the pre-operative diagnosis.

STATISTICAL ANALYSIS: The analysis was made by the SPSS program for Windows version 21.0. Categorical variables are presented as absolute numbers and percentage. Continues variables are presented as mean±SD. Unpaired 't' test was used to compare normally distributed continuous variables. A ROC analysis was calculated to determine optimal cut-off values for Alvarado score, TLC and TSB. The sensitivity, the specificity and AUC was calculated to analyze the diagnostic value of all these markers, P value less than 0.05 was considered statistically significant.

RESULTS: Initially various demographic variables were assessed and documented. The data reveals that out of 100 cases studied, 61 were males and 39 females.

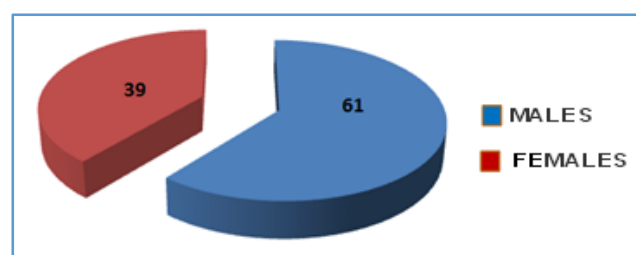


Fig. 1

The observed age pattern found in the range of 5 to 67 years with a mean of 36 years.

Maximum incidence of cases was noticed in the age group of 21 to 40 years (45 out of 100), whereas only three cases were reported after the age of 60yrs.

AGE DISTRIBUTION

• Less than 10 yrs	10
• 10 to 20yrs	24
• 21 to 40yrs	46
• 41 to 60yrs	17
• More than 60 yrs	03

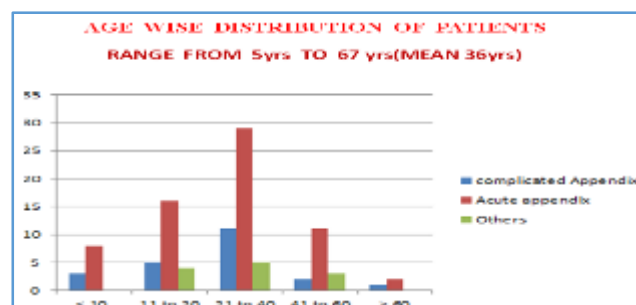


Fig. 2

Patients who were admitted before 24 hours were referred as "early group," whereas the others admitted after 24 hours as "late group."

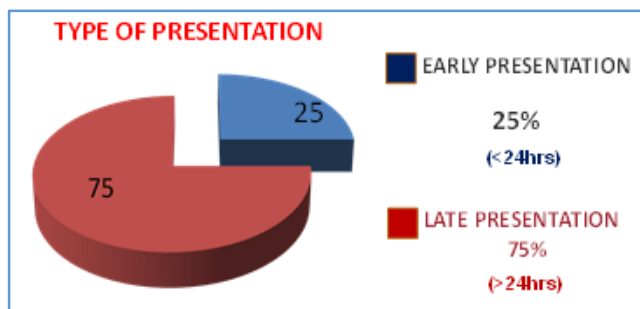


Fig. 3

Out of 100 patients, 6 patients were managed conservatively as their Alvarado score was 4 and below and 6 patients had normal appendix intra-operatively and confirmed by histopathology. Out of the rest 88 patients refer to as positive cases, 22 patients had complicated appendix like gangrene, perforation and impending perforation in which majority was gangrenous type with more female preponderance. Remaining 66 patients had inflammation of varying degree like (low/moderate/high) in which more-number of cases belongs to low degree of inflammation with high number of female sex.

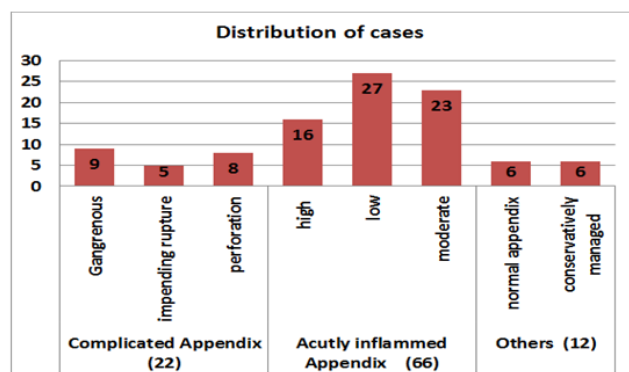


Fig. 4

Variables	No. of Cases	Sex		Time	
		Male	Female	< 24hrs	> 24hrs
Complicated Appendix (22)					
(a) Gangrenous	9	4	5	0	9
(b) Impending rupture	5	3	2	0	5
(c) Perforation	8	2	6	0	8
In combination (a+b+c)	22	9	13	0	22
Acutely inflamed Appendix (66)					
(a) High	16	5	11	3	13
(b) Low	27	9	18	12	15
(c) Moderate	23	9	14	6	17
In combination (a+b+c)	66	23	43	21	45
Others (12)					
(a) Normal appendix	6	4	2	2	4

(b) Not operated	6	3	3	2	4
In combination (a+b)	12	7	5	4	8
Grand Total	100	39	61	25	75

Table 1: Sex differentiation and presentation of various variables in time course

Alvarado Score: After admission, all the patients were subjected to Alvarado scoring system, based on the criteria given in Table below and their distribution was noted according to the score, in which majority of cases were noted with the score of 7 with 35%. Sensitivity was 63.6%, specificity 80%, PPV 51.8%, NPV 86.8%, AUC 0.825, t-test 5.673, p value 0.000.

Table 2: Alvarado Score:

Alvarado score (100 patients)			
10	3		
9	12	Sensitivity	63.6% ,
8	18	Specificity	80% ,
7	35	PPV	51.8% ,
6	21	NPV	86.8% ,
5	5	AUC	0.825 ,
4	3	t-test	5.673 ,
3	2	p value	0.000 .
2	1		

TLC: TLC was done for all patients who were admitted. In 22 gangrenous/perforated cases TLC was raised in 13 cases and normal in 9 cases (<10,000 considered as normal). Out of 66 inflamed cases, TLC was raised in 33 and normal in 33. In 6 cases where appendix was normal (found in laparotomy and histopathology) TLC was not raised and 6 cases which are treated conservatively, 3 patients had raised TLC and 3 had normal TLC. Sensitivity was 50%, Specificity 87.07%, PPV 47.8%, NPV 83.07%, AUC was 0.645, t-test 2.464, p value 0.016.

TSB: TSB was done for all patients, out of 22 gangrenous/perforated cases, TSB was HIGHLY elevated in 17 cases and normal in 5 cases. Out of 66 inflamed cases, TSB was raised in 31 and normal in 35. Out of 6 cases of normal appendix (found in laparotomy and histopathology), TSB was within normal limits. Of 6 cases which were treated conservatively (<4 Alvarado score) TSB was raised in 2 cases and normal in 4 cases. Sensitivity 81.8%, Specificity 81.8%, PPV 60%, NPV 93.1%, AUC 0.908, t-test 7.521, p value 0.000.

Variables	No. of Cases	TLC		TBC	
		Normal	Raised	Normal	Raised
Complicated Appendix					
(a) Gangrenous	9	2	7	2	7
(b) Impending rupture	5	2	3	1	4
(c) Perforation	8	5	3	2	6
In combination (a+b+c)	22	9	13	5	17
Acute Inflamed Appendix					
(a) High	16	4	12	6	10
(b) Low	27	21	6	16	11
(c) Moderate	23	8	15	13	10
In combination (a+b+c)	66	33	33	35	31
Others					
(a) Normal appendix	6	6	0	6	0
(b) Not operated	6	3	3	4	2
In combination (a+b)	12	9	3	10	2
Grand Total	100	60	52	60	52

Table 3

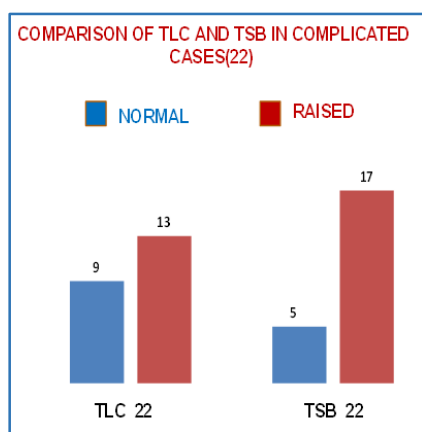


Fig. 5

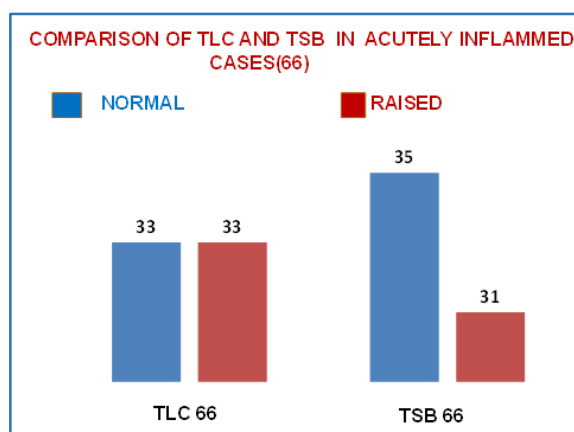


Fig. 6

	Gangrenous		Inflammatory		t - Test	P Value
	Mean±SD	Min-Max	Mean ±SD	Min- Max		
TLC	12209.09±685.73	6500.00-20000.00	10254.54±3056.50	4900.00-19000.00	2.464	0.016
TBC	3.13±1.85	0.97 - 8.60	1.20±0.56	0.36 - 3.67	7.521	0.000
AI Score	8.18±1.09	7.00 - 10.00	6.69±1.05	5.00 - 9.00	5.673	0.000

Table 4: T-test and P-value of different parameters

Sensitivity, specificity, positive and negative predictive value of different. Parameters, AUC-Area Under Curve.

	AUC	Cut off	Sensitivity	Specificity	PPV	NPV
TLC	0.645	12550	50%	81.8%	47.8%	83.07%
TBC	0.908	1.65	81.8%	81.8%	60%	93.1%
ALV SCORE	0.825	7.5	63.6%	80%	51.8%	86.8%

Table 5

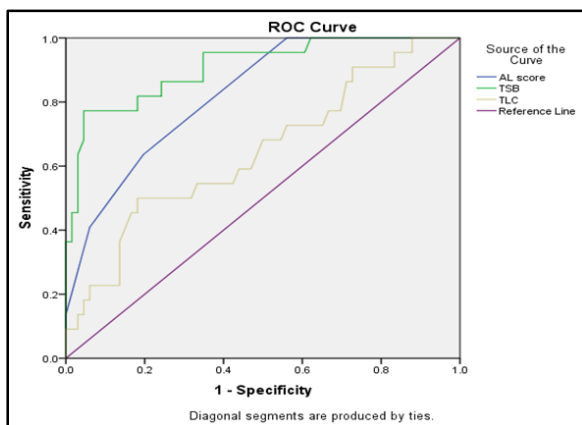


Fig. 7

Area under the curve

Test Result Variable (s)	Area	Std. Error. ^a	Asymptotic Sig. ^b	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
AL score	.825	.046	.000	.734	.916
TSB	.908	.037	.000	.836	.981
TLC	.645	.070	.043	.508	.782

Table 6: Independent Samples Test

The test result variable(s): AL score, TSB, TLC has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.

- a. Under the nonparametric assumption.
- b. Null hypothesis: true area = 0.5.

DISCUSSION: Since acute appendicitis is a surgical emergency, most of the cases require immediate appendectomy. Necessary treatment modalities are required quickly to reduce mortality rates. (Stephens PL, Mazzucco JJ).⁴ Therefore timely clinical decision is essential for better diagnosis (Ohmann C, Yang Q, Franke C).¹⁹ with the evidence of history and clinical examination. Several studies clearly demonstrated that surgeon’s timely decision is mandatory because unnecessary surgical intervention carries the risk of morbidity and mortality (Ohmann C, Yang Q, Franke C).¹⁹ The diagnosis of acute appendicitis is mainly clinical, though ultrasound and CT scan can be helpful. Sometimes the correct diagnosis could hardly be made. (Hoffman JO, Rasmussen O).¹⁶ Diagnostic accuracy regarding appendicitis also depends on the experience of surgeon, yet the need for supportive measures is always there. (Alvarado A In).¹³ CT scan may resolve the issue supported by ultrasonography and assessment of C-reactive protein levels (Terasawa T, Blackmore CC, Bent S, Kohlwes RJ).²⁰ However, for the better outcome various scoring systems have been considered (Abdeldaim Y, Mahmood S, McAvinchey D).²¹ Numerous studies have revealed various scoring systems for the better diagnosis of appendicitis (Brigand C, Steinmetz JP, Rohr S, J Chir Paris).²² Few studies highlighted the importance of Alvarado score to assess the clinical diagnosis of acute appendicitis.

Alvarado scoring system (Table-2) works mainly based on the history, physical examination and few laboratory investigations (Abdeldaim Y, Mahmood S, McAvinchey D).²¹ which remains the mainstay of correct diagnosis of acute appendicitis. (Ohmann C, Yang Q, Franke C and Khan I, Rehman A).¹⁹

According to Chan et al. 2001, out of 100 subjects, 83% were suspected with acute appendicitis and underwent appendectomy of those operated, 8 subjects were found to have normal appendix and others were associated with symptoms related to pathology. The rate of negative appendectomy found to be representing with a percentage of 9.6% Crnogorac, 2001; Gwynn, 2001; Khan, 2005; and Denizbassi, 2003).

Similarly, various studies also presented comparable data and also represented the same rates of incidence related to positive and negative appendectomy (Kalan M, Talbot D, Cunliffe WJ, Rich AJ).²³ Thus, our study is correlated to other studies demonstrating the sensitivity, positive and negative predictive value of Alvarado scoring system. In our series, out of 100 patients 6 patients underwent appendectomy (as the Alvarado score was 6 and above) and were found normal on histopathology. (PPV 51.8% and NPV 86.8%).

In this study, serum bilirubin was highly raised in 17 of 22 gangrenous/perforated cases. In 66 inflamed cases of varying degrees, TSB was moderately raised in 31 cases and normal in 35 cases. Out of 6 patients who were treated conservatively, TSB was moderately raised in 2 cases and normal in 4 cases. TSB was within normal limits in 6 cases, who were operated and found normal appendix. (As the Alvarado score was 6 and above). The raise of TLC was only in 13 of 22 gangrenous/perforated patients. Whereas, TSB was raised in 17 (ranged from 2.10 to 8.60) cases, which was a significant and reliable finding.

As we have selectively taken the cases of appendicitis without any other comorbidities (Alcoholic and liver diseases, viral hepatitis, other viral infections, malignancies, hemolytic diseases and history of drug abuse), etc. raise of Serum Bilirubin could not be attributed to any other cause except the inflamed appendix. It is known for many years that patients with wide variety of non-hepatic infections can develop Cholestasis. It is not uncommon to find raised conjugated bilirubin levels, in patients with various infections, common ones being gut derived organisms. Sepsis associated jaundice is seen in adults with significant frequency. The link of infection to cholestasis may be due to cytokines mainly TNF@, IL 1B, IL 6 or microsomal TLR 2 or TLR 4 agonists. Liver targets primarily include hepatocytes, but also extended to Kupffer cells, cholangiocytes, endothelial cells, stellate cells. It seems there is a link of endothelium induced cytokines to cholestasis.²⁴ (Ref: Seminars on liver diseases – Role of inflammation in cholestasis and basic aspects. Astrid Kostersphd/Saul J. Karpen, MD, PhD; Seminars on liver diseases 2010, 30 (2 186–194).²⁵

CONCLUSION: The present study clearly reveals significance of raise of TSB for the diagnosis of acute appendicitis, which is based on mainly clinical evaluation. Moreover, the assessment of TSB is simple, very easy and cheap complementary aid for supporting the diagnosis of acute appendicitis, particularly in diagnosing impending gangrenous/perforated cases, so that complications like rupture or peritonitis can be avoided.

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