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# Clinicopathological Correlation of Hyperbilirubinemia as a Predictor of Perforation in Acute Appendicitis

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**Abstract:** Appendicular Perforation rates range from 4% to 45%, death rate range from 0.17% to 7.5% and in patients with acute appendicitis may cause a variety of potentially life threatening complications and is responsible for a considerable amount of morbidity. In this study we found that hyperbilirubinemia has a clear edge over the others when used to diagnose established perforation (diagnostic accuracy of 92% and PPV of 66.67%). In this scenario, leukocytosis has high diagnostic accuracy (76.67%) but low positive predictive value (25.71%). When used to diagnose cases with established perforation plus impending perforation i.e., gangrene the positive predictive value of CRP-test shoots up (57.14%). But it still remains lower than that of leukocytosis (77.14%) and hyperbilirubinemia (66.67%). However, its diagnostic accuracy (78%) surpasses that of bilirubin levels (76%) and comes second only to leukocytosis (84.67%). High specificity of hyperbilirubinemia (~95%) and leukocytosis (80-92%) in diagnosing established perforation as well as perforation or impending perforations taken together, implies that the absence of hyperbilirubinemia and leukocytosis virtually rules out the presence of perforation/impending perforation. In addition, we found a statistically significant correlation between detection of E. coli in abdominal fluid/pus culture and presence of hyperbilirubinemia (Uncorrected Chi-Square = 9.257 and Mid-P exact: P-value 0.001606).

**Keywords:** Acute Appendicitis, Appendicular Perforation, Hyperbilirubinemia, CRP levels, ALVARADO score and degree of Leucocytosis

## INTRODUCTION

Acute Appendicitis is a common cause of abdominal pain in all ages. Appendicitis is so common that appendectomy is the most frequently performed urgent abdominal operation [1]. However, it is often a perplexing diagnostic problem during the early stages of the disease. In many cases, usually during the prodromal phase, its clinical manifestations may be vague and uncertain. Failure to make an early diagnosis is a primary reason for the persistent rate of morbidity and mortality [2].

Perforation rates range from 4% to 45%, and death rate range from 0.17% to 7.5% as reported by Alfredo Alvarado, in the year 1986 [2]. Appendicular perforation in patients with acute appendicitis may cause a variety of potentially life threatening complications and is responsible for a considerable amount of morbidity. The number of unnecessary laparotomies, particularly in women, may be as high as 45%. The overall "negative appendectomy rate", ranges from 14% to 75% [2]. So, the accurate preoperative diagnosis of acute appendicitis continues to be a challenge to the surgeons [3, 4].

A variety of approaches [5] have been described to increase the diagnostic accuracy and to decrease the negative appendectomy rate, particularly where the symptoms and signs are not so promising, including the development of predictive scoring systems, computer-aided diagnosis, intensive in-house observation, the use of plain abdominal films and diagnostic laparoscopy and recently, Graded Compression Ultrasonography and Computed Tomography (CT) scan.

Among the various scoring systems, The ALVARADO SCORE is most useful. It is a ten point scoring system, designed by Alfredo Alvarado, USA, in 1986 [2], and is based on three symptoms, three signs and two laboratory findings:

| ALVARADO SCORE[37] | | APPENDICITIS INFLAMMATORY RESPONSE SCORE[38,39] | |
|---|---|---|---|
| **Findings** | **Points** | **Findings** | **Points** |
| Migratory right iliac fossa pain | 1 | Vomiting | 1 |
| Anorexia | 1 | Pain in the right inferior fossa | 1 |
| Nausea or vomiting | 1 | Rebound tenderness or muscular defense | |
| Tenderness: right iliac fossa | 2 | Light | 1 |
| Rebound tenderness right iliac fossa | 1 | Medium | 2 |
| Fever ≥36.3°C | 1 | Strong | 3 |
| Leukocytosis ≥10 × $10^9$ cells/L | 2 | Body temperature ≥38.5°C | 1 |
| Shift to the left of neutrophils | 1 | Polymorphonuclear leukocytes | |
| | | 70%–84% | 1 |
| | | ≥85% | 2 |
| | | White blood cell count | |
| | | 10.0–14.9 × $10^9$ cells/L | 1 |
| | | ≥15.0 × $10^9$ cells/L | 2 |
| | | C-reactive protein concentration | |
| | | 10–49 g/L | 1 |
| | | ≥50 g/L | 2 |
| Score: <3: Low likelihood of appendicitis<br>4–6: Consider further imaging<br>≥7: High likelihood of appendicitis | | Score: 0–4: Low probability. Outpatient follow-up.<br>5–8: Indeterminate group. Active observation or diagnostic laparoscopy.<br>9–12: High probability. Surgical exploration. | |

**Fig-1: ALVARADO SCORE**

Thus, as of now, all we have, at our disposal for preoperative diagnosis of perforation are CT scan, USG [6-13], routine blood examination along with thorough clinical examination (including scoring systems). The former are costly and difficult to arrange in our set-up on an urgent basis and the latter demands expertise. The purpose of this study is to establish a relation between hyperbilirubinemia, CRP, total leukocyte counts and clinic pathological assessment of patients with acute appendicitis so as to ascertain whether hyperbilirubinemia can be used as an accurate and simple predictor of perforation in acute appendicitis.

## MATERIALS AND METHODS

This was an institution-based, prospective, observational and analytical study conducted in Department of Surgery, Medical College, Kolkata, India from January 2010 to June 2011 (18 months). Informed consent was taken from all the patients. The study got clearance from Institutional Ethical Committee. Sample size was 150. They were clinically assessed through history and examination. MANTRELS scoring of patients was done. Serum bilirubin levels were assessed along with CRP levels and degree of leukocytosis. Intraoperative findings were noted along with postoperative histopathological examination. Finally, a correlation among all the above findings was tried to be drawn so as to see if hyperbilirubinemia can be used as a predictor of perforation in acute appendicitis.

### Inclusion Criteria

The following patients were included in the study population:

- All patients admitted in Emergency Surgical Ward with acute appendicitis with or without complication.

### Exclusion Criteria

The following patients were excluded from the study population:

- History of appendectomy.
- Alcoholism.
- H/O viral hepatitis.
- Gilbert's disease, Crigler Najjar Syndrome.
- Dubin Johnson Syndrome, Rotor Syndrome.
- BRIC (Benign recurrent intra-hepatic cholestasis) and other documented biliary disease.
- Hemolytic or liver diseases associated with hyperbilirubinemia.

Random selection of approximately 150 patients with acute appendicitis or appendicular perforation was done from patients admitted in MCH, Kolkata using the inclusion and exclusion criteria. Clinical assessment and evaluation of serum bilirubin along with CRP and total leukocyte count was done. Intraoperative findings and biopsy reports was noted. Tabulation of data and graphical presentation using charts and tables was done. Appropriate statistical tests relevant to data were performed to come to a conclusion

## RESULTS

A total of 150 patients were studied and results were analyzed.

### Descriptive Statistics

### Final Diagnosis

Among 150 patients, 99 (66%) patients had simple (catarrhal/suppurative) appendicitis. 24 (16%) patients had gangrenous appendicitis. Appendicular perforation was present in 18 (12%) cases. Lump was present in 6 (4%) patients. Abscess was present in 3 (2%) cases.

**Table-1: Descriptive Statistics of Final diagnosis of patients.**

| Classification (after HPE) | Number | Percentage |
|---|---|---|
| Simple (catarrhal + suppurative) | 99 | 66 |
| Gangrene | 24 | 16 |
| Perforation | 18 | 12 |
| Lump | 6 | 4 |
| Abscess | 3 | 2 |

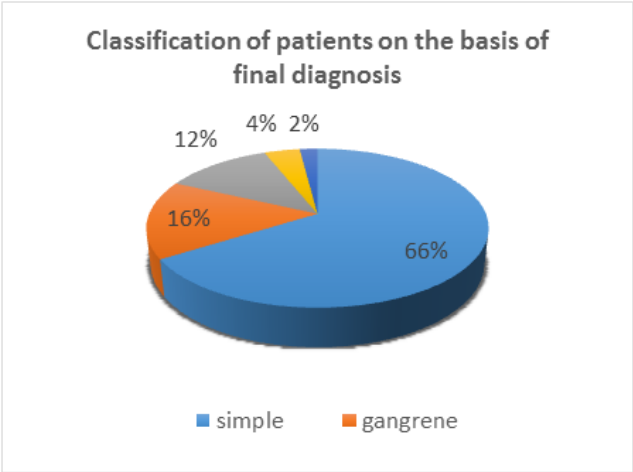


**Fig-2: Pie Chart of distribution of patients on the basis of final diagnosis**

**Sex**

There were 89 females and 61 males out of 150 patients. The male: female ratio was 61:89, approximately 2:3, the ratio for simple appendicitis being 3:8 (27:72). Gangrenous variety was 3 (18/6) times more common in males than females. Appendicular perforation was 5 (15/3) times more common in males than females. Lumps and abscesses were equivocal in both the sexes.

**Table-2: Descriptive Statistics of Sex**

| Group | Male | Female | Total |
|---|---|---|---|
| Simple (catarrhal + suppurative) | 27 (27.27%) | 72 (72.73%) | 99 |
| Gangrene | 18 (75%) | 6 (25%) | 24 |
| Perforation | 15 (83.33%) | 3 (16.67) | 18 |
| Lump | 3 (50%) | 3 (50%) | 6 |
| Abscess | 1 (33.33%) | 2 (66.67%) | 3 |
| Total | 61 (40.67%) | 89 (59.33%) | 150 |

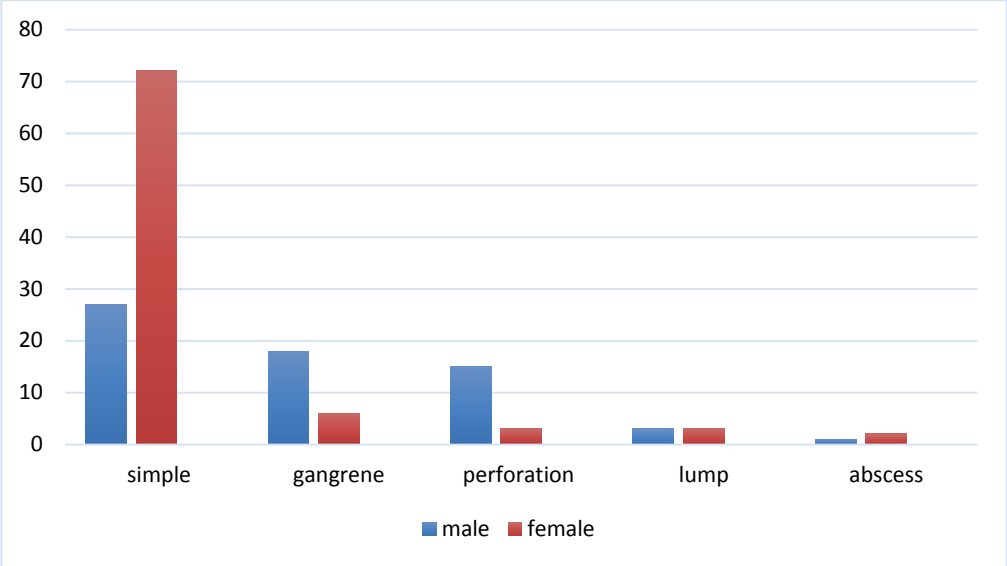


**Fig-3: Bar diagram representing distribution of Sex.**

**Age**

The mean and median ages are comparable in all the groups, except for the gangrene group due to greater incidence of gangrene in extremes of ages. Perforation and abscess are more common in higher age groups (mean age being 42.83 years and 44 years respectively) compared to simple appendicitis, gangrene and lump (mean age being 25.17 years, 28.88 years and 33.50 years respectively).

**Table-3: Descriptive Statistics of Age.**

| Group | Mean age (years) | Median age (years) | Range (years) |
|---|---|---|---|
| Simple (catarrhal + suppurative) | 25.17 | 25 | 9-50 |
| Gangrene | 28.88 | 24.5 | 10-70 |
| Perforation | 42.83 | 42.5 | 27-60 |
| Lump | 33.50 | 33.50 | 29-38 |
| Abscess | 44.00 | 44.00 | 40-48 |

**Fig-4: Bar diagram showing mean and median ages for various groups (in years).**

**Pre-hospitalization duration of symptoms**

Lump and abscess seem to present much later (with mean durations of 12 and 7 days respectively) from onset of symptoms than simple appendicitis (2.83 days). Gangrenous cases present after 3.81 days of symptoms.

However, cases of perforation with generalized peritonitis seem to present rather early (2.5 days). This may appear to be fallacious but this could be because of more clear-cut and severe symptoms associated with this pathology.

**Table-4: Descriptive Statistics of pre-hospitalization duration of symptoms**

| Group | Avg. duration(days) | Range(days) |
|---|---|---|
| Simple (catarrhal + suppurative) | 2.83 | 0.5-7 |
| Gangrene | 3.81 | 0.5-10 |
| Perforation | 2.5 | 1-3 |
| Lump | 12 | 10-14 |
| Abscess | 7 | 3-14 |

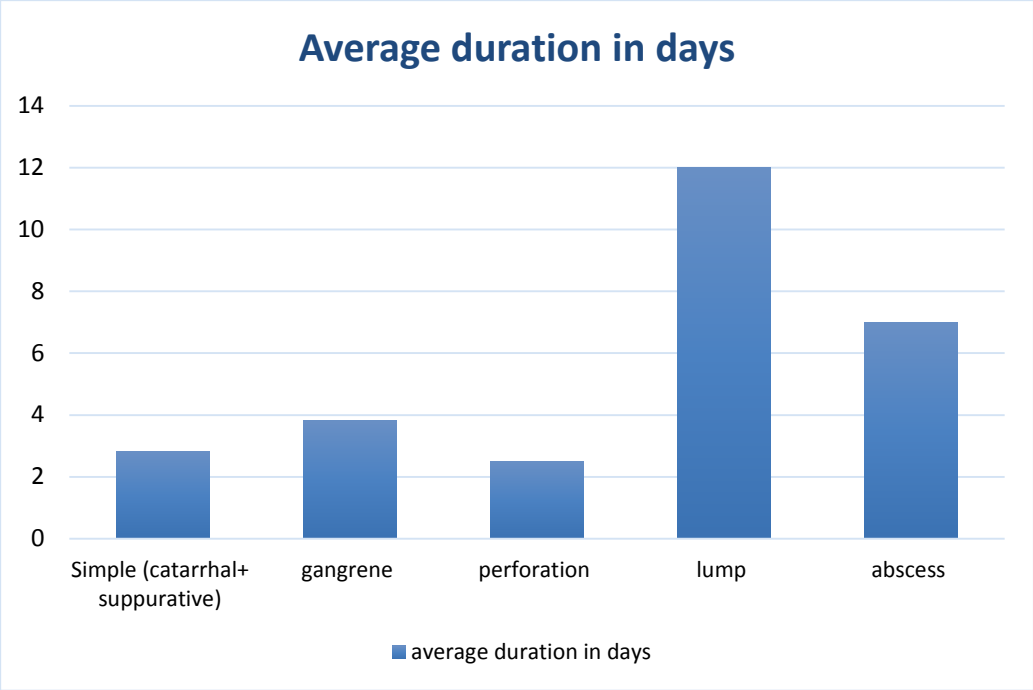


**Fig-5: Bar diagram showing descriptive statistics of pre-hospitalization duration of symptoms.**

**Bilirubin Levels**

The mean and median bilirubin levels (1.215 and 1.195 respectively) were both significantly high in cases with established perforation.

**Table-5: Descriptive Statistics and analysis of bilirubin levels of the different groups.**

| Group | Mean bilirubin (mg/dl) | Median (mg/dl) | Std. deviation | Range |
|---|---|---|---|---|
| Simple (catarrhal + suppurative) | 0.687 | 0.7 | 0.224 | 0.39-1.5 |
| Gangrene | 0.773 | 0.8 | 0.156 | 0.5-.98 |
| Perforation | 1.215 | 1.195 | 0.41 | 0.6-1.9 |
| Lump | 0.75 | 0.75 | 0.055 | 0.7-0.8 |
| Abscess | 0.6 | 0.6 | 0.2 | 0.4-0.8 |

The statistical significance of the above are as follows:

1) Variation between groups:
   F-statistics: 18.628,
   P-value = 0.00000000000224828

2) Test for equality of variance:
   Chi square = 29.9286,
   P-value = 0.0000050611

The mean values for serum bilirubin for the gangrene (0.773 mg/dl) and lump (0.75mg/dl) groups were also higher than patients with simple appendicitis (0.687) but the values are not higher than normal physiological levels of serum bilirubin (0.3-1gm /dl).

The cases of appendicular abscesses showed lower levels (0.6mg/dl) probably because they had already been treated conservatively before referral to our center in all the cases.

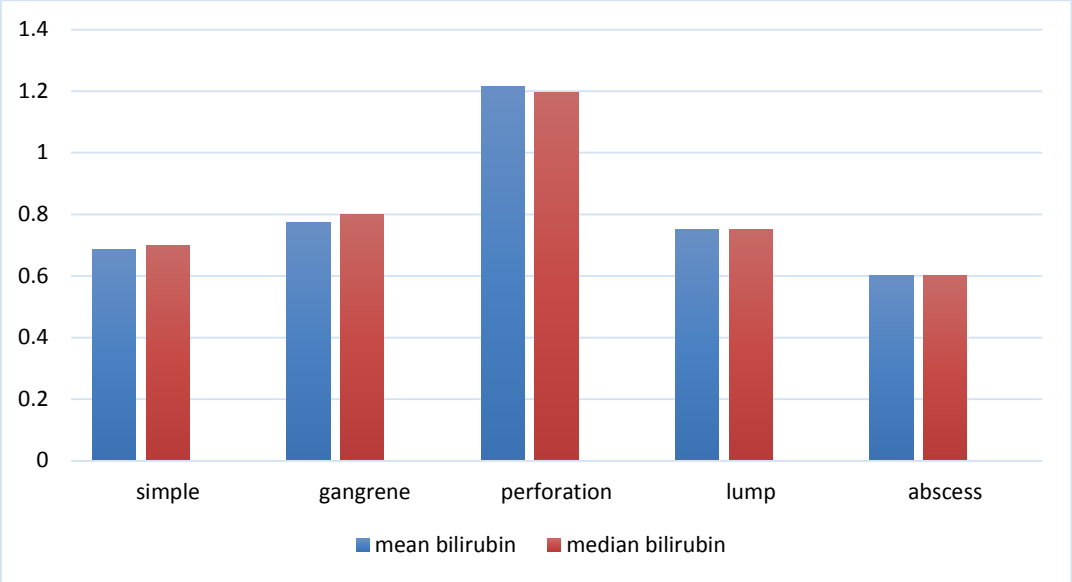


**Fig-6: Bar diagram representing distribution of bilirubin levels of the different groups.**

**Hyperbilirubinemia**

12 (66.67%) among 18 patients of perforation had hyperbilirubinemia. But none of those with a gangrene/impending perforation had hyperbilirubinemia. 6 (6.06%) out of 99 patients with simple appendicitis had hyperbilirubinemia. None with lump or abscess had hyperbilirubinemia.

**Table-6: Distribution of patients with hyperbilirubinemia in various groups**

| Hyperbilirubinemia (>1mg/dl) | Perforated group | Gangrenous | Simple | Lump | Abscess |
|---|---|---|---|---|---|
| yes | 12 (66.67%) | 0 | 6(6.06%) | 0 | 0 |
| no | 6(33.33%) | 24(100%) | 93 (93.94%) | 6 (100%) | 3 (100%) |

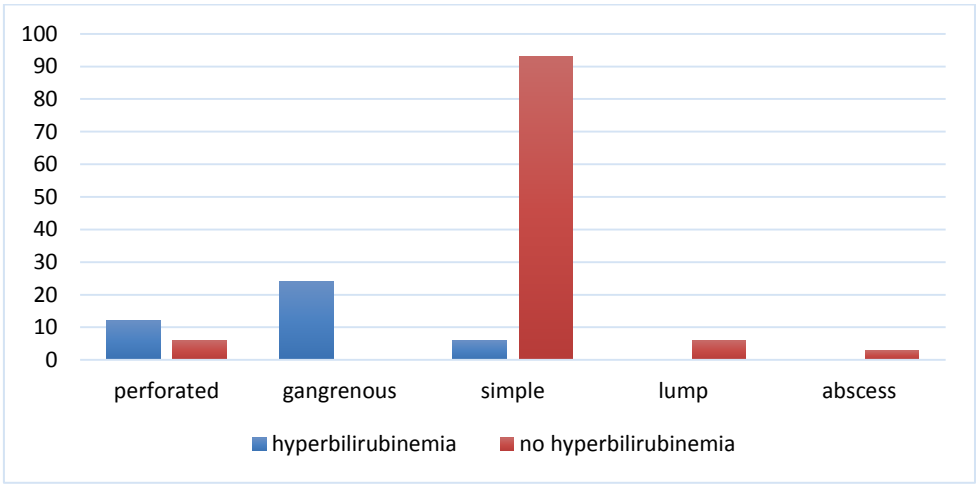


**Fig-7: Bar Diagram showing distribution of patients with hyperbilirubinemia in various groups**

**Hyperbilirubinemia for Perforation vs. Non-perforated group**

**Table-7: Distribution of hyperbilirubinemia in perforation vs. mon-perforated group**

| Perforation | Number | Mean Bilirubin | Std. Deviation |
|---|---|---|---|
| Yes | 18 | 1.215 | 0.41 |
| No | 132 | 0.704 | 0.21 |

18 (12%) patients had perforation with a mean bilirubin level of 1.215 mg/dl. 132 (88%) cases were non-perforated ones with a mean bilirubin level of 0.704 mg/dl. Statistical significance of above data:

Equal variance: *t* statistics = 8.41983, P-value < .0000001

Unequal variance: *t* statistics = 5.19566, P-value = 0.00006091

Test for equality of variance: *t* statistics = 3.81179, P-value = 0.00001127

**Hyperbilirubinemia for perforation and impending perforation (gangrene) vs. others**

**Table-8: Distribution of hyperbilirubinemia in perforation and impending perforation (gangrene) vs. others**

| Perforation (established + impending) | Number | Mean Bilirubin | Std. Deviation |
|---|---|---|---|
| Yes | 42 | 0.962 | 0.364 |
| No | 108 | 0.688 | 0.217 |

42 (28%) patients either had established perforation or impending perforation with a mean bilirubin level of 0.962 mg/dl. 108 (72%) patients belonged to other groups and had a mean bilirubin level of 0.688.

Statistical significance of the above:

Equal variance: *t* statistics = 5.66476, P-value < .0000001

Unequal variance: *t* statistics = 4.57259, P-value = 0.00002929

Test for equality of variance: *t* statistics = 2.81374, P-value = 0.00002176

**Validation of serum Hyperbilirubinemia as a test to diagnose appendicular perforation**

**Table-9: Validation of serum Hyperbilirubinemia as a test to diagnose appendicular perforation**

| Hyperbilirubinemia | Perforation present | Perforation absent |
|---|---|---|
| yes | 12 | 6 |
| no | 6 | 126 |

Sensitivity = {12/ (12+6)} = 66.67%

Specificity = {126/ (126+6)} = 95.45%

Positive Predictive Value = {12/ (12+6)} = 66.67%

Negative Predictive Value = {126/ (126+6)} = 95.45%

Diagnostic Accuracy = 92%

**Validation of serum Hyperbilirubinemia as a test for detecting appendicular perforation plus impending perforation (gangrene)**

**Table-10: Validation of serum Hyperbilirubinemia as a test for detecting appendicular perforation plus impending perforation (gangrene)**

| Hyperbilirubinemia | Perforation or gangrene | Others |
|---|---|---|
| yes | 12 | 6 |
| no | 30 | 102 |

Sensitivity = {12/ (12+30)} = 28.57%

Specificity = {102/ (102+6)} = 94.44%

Positive Predictive Value = {12/ (12+6)} = 66.67%

Negative Predictive Value = {102/ (102+30)} = 77.27%

Diagnostic Accuracy = 76%

**Relation between isolation of E. coli in pus/abdominal fluid and serum hyperbilirubinemia**

**Table-11: Relation between isolation of E. coli in pus/abdominal fluid and serum hyperbilirubinemia**

| Group | E. coli +ve | Hyperbilirubinemia | Both +ve |
|---|---|---|---|
| Simple (catarrhal + suppurative) | 3 | 6 | 3 |
| gangrene | 0 | 0 | 0 |
| perforation | 15 | 12 | 12 |
| lump | 0 | 0 | 0 |
| abscess | 3 | 0 | 0 |
| overall | 21 | 18 | 15 |

15 of the 18 (83.33%) patients with hyperbilirubinemia showed a positive culture for E. coli. Of the 21 E. coli positive cases, 15 (71.43%) had hyperbilirubinemia.

**Chi-square association between E. coli isolation and hyperbilirubinemia**

**Table-12: Chi-square association between E. coli isolation and hyperbilirubinemia**

| E. coli | Hyperbilirubinemia | No hyperbilirubinemia |
|---|---|---|
| Yes | 15 | 6 |
| No | 3 | 12 |

Among 150 patients, only 36 (24%) had abdominal fluid or pus which was cultured.15 (83.33%) out of 18 patients with hyperbilirubinemia showed positive E. coli culture. Of 18 patients without hyperbilirubinemia E. coli was isolated in the pus/abdominal fluid culture of 6 (33.33%) patients.

Uncorrected Chi-Square = 9.257 (P-value=0.001173)
Mid-P exact: P-value 0.001606

In all the 18 cases of perforation, fluid/pus was sent. 15 showed E. coli and 3 showed no growth. Of the 15 E. coli +ve cases 12 showed hyperbilirubinemia. Rest 3 were showing bilirubin levels equal to the higher limit (1 mg/dl). All the 3 cases of appendicular abscess however showed E. coli but normal bilirubin levels. In 9 cases of simple appendicitis, fluid/pus was sent for c/s. 6 were sterile. 3 showed E. coli. Those 3 also had hyperbilirubinemia. In 6 cases of gangrene fluid/pus was cultured. None yielded E. coli.

**Serum C - reactive protein levels**

The CRP levels in each group were scattered over a huge range. So, the mean and median values were not close. However, the mean and median values of CRP levels were consistently and significantly higher in the groups with perforation (75.27 mg/l and 38.3 mg/l respectively) and gangrene (66.99 mg/l and 43.86mg/l respectively). Some cases with perforation and gangrene showed lower levels of CRP.

The cases with lump and abscess had higher mean (14.55 mg/l and 18.27 mg/l respectively) and median (14 and 18.27 mg/l respectively) values of CRP levels than the group with simple appendicitis (with mean CRP = 12.59 mg/l and median CRP = 3.67 mg/l), but not as high as in the group with perforation and gangrene. Actually all the cases of lump and abscess were referred from other facilities where they had been treated conservatively for some time. This could be the reason for a relatively milder clinical/biochemical picture.

**Table-13: Analysis of serum C - reactive protein levels**

| Group | Mean CRP level(mg/l) | Median CRP level(mg/l) | Range (normal<6mg/l) |
|---|---|---|---|
| Simple (catarrhal+ suppurative) | 12.59 | 3.67 | 1-106 |
| gangrene | 66.99 | 43.86 | 6.1-249 |
| perforation | 75.27 | 38.3 | 5.8-234.4 |
| lump | 14.55 | 14 | 5.1-24 |
| abscess | 18.27 | 18.27 | 16-20.54 |

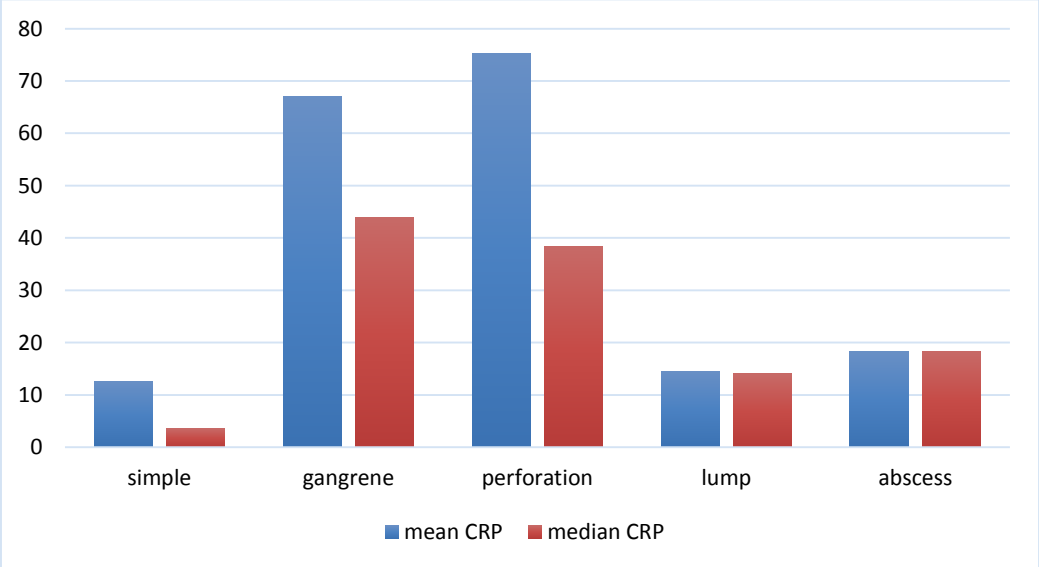


**Fig-8: Analysis of serum C - reactive protein levels**

**Association of raised CRP levels with the various groups**

**Table-14: Association of raised CRP levels with the various groups**

| Raised CRP levels | Perforated group | Gangrenous | Simple | Lump | Abscess |
|---|---|---|---|---|---|
| yes | 12 (66.67%) | 24 (100%) | 21(21.21%) | 3 (50%) | 3(100%) |
| no | 6 (33.33%) | 0 | 78 (78.79%) | 3 (50%) | 0 |

12 (66.67%) out of 18 patients with perforation had raised CRP levels. All patients with gangrene had raised CRP levels. 21 (21.21%) out of 99 patients with simple appendicitis had raised CRP levels. All cases of abscesses had raised CRP levels. Lumps had equivocal results.

**Validation of raised CRP levels as a test to detect appendicular perforation**

**Table-15: Validation of raised CRP levels as a test to detect appendicular perforation**

| Raised CRP levels | Perforation Present | Perforation Absent |
|---|---|---|
| Yes | 12 | 51 |
| No | 6 | 81 |

Sensitivity = {12/(12+6)} = 66.67%
Specificity = {81/(81+51)} = 61.36%
Positive Predictive Value = {12/(12+51)} = 19.05%
Negative Predictive Value = {81/(81+6)} = 93.1%
Diagnostic Accuracy = 62%.

**Validation of raised serum CRP levels as a test to detect perforation plus gangrene (impending perforation)**

**Table-16: Validation of raised serum CRP levels as a test to detect perforation plus gangrene (impending perforation)**

| Raised CRP levels | Perforation or gangrene | Others |
|---|---|---|
| YES | 36 | 27 |
| NO | 6 | 81 |

Sensitivity = {36/(36+6)} = 85.71%
Specificity = {81/(81+27)} = 75%
Positive Predictive Value = {36/(36+27)} = 57.14%
Negative Predictive Value = {81/(81+6)} = 93.1%
Diagnostic Accuracy 78%

**Alvarado scores in the various groups**

The Alvarado score in the perforation (mean and median both being 8) and gangrenous (mean being 8.125 and median being 8) appendicitis groups were clearly higher than the overall average that was just below 6. So for all practical purposes it can be presumed that for all cases of acute appendicitis an Alvarado score of 6 or more may be diagnostic. Scores below 6 indicate equivocal diagnosis. The patients in the simple appendicitis group had a mean Alvarado score of 5.1 and a median score of 5. Patients with appendicular lump had both mean and median Alvarado score of 5.5. Patients with appendicular abscess had a mean Alvarado score of 5.33 and a median score of 5. An overall range of scores from 3 to 10 was observed to be present.

**Table-17: Descriptive statistics of Alvarado scores in the various groups**

| Group | Mean score | Median score | Range |
|---|---|---|---|
| Simple (catarrhal+ suppurative) | 5.10 | 5 | 3-7 |
| gangrene | 8.125 | 8 | 6-10 |
| perforation | 8 | 8 | 5-10 |
| lump | 5.5 | 5.5 | 5-6 |
| abscess | 5.33 | 5 | 5-6 |
| overall | 5.95 | 5.5 | 3-10 |

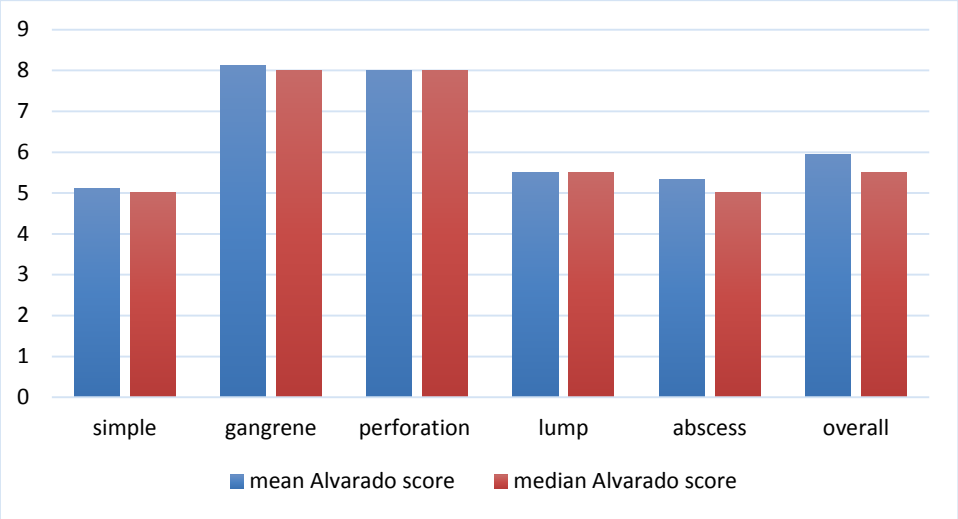


**Fig-9: Analysis of Alvarado scores in the various groups.**

**Number of patients with above average Alvarado scores in each group**

**Table-18: Descriptive statistics of above average Alvarado scores in the various groups**

| Alvarado score above overall average | Perforated group | Gangrenous | Simple | Lump | Abscess |
|---|---|---|---|---|---|
| yes | 15 (83.33%) | 24 (100%) | 69 (69.7%) | 3 (50%) | 1 (33.33%) |
| no | 3 (16.67%) | 0 | 30 (30.3% | 3 (50%) | 2 (66.67%) |

15 (83.33%) out of 18 patients with perforation had above average Alvarado score. All gases of gangrene had above average Alvarado scores. 69 (69.7%) out of 99 cases were having above average Alvarado score. In lumps and abscesses results were equivocal probably due to walling of i.e. localization of inflammation or probably because such cases were mostly referred from other facilities where they had already received a course of conservative management.

**Validation of Alvarado score as a test to diagnose perforation**

**Table-19: Validation of Alvarado score as a test to diagnose perforation**

| Above average Alvarado score | Perforation present | Perforation absent |
|---|---|---|
| yes | 15 | 97 |
| no | 3 | 35 |

Sensitivity = {15/(15+3)} = 83.33%
Specificity = {35/(35+97)} = 26.52%
Positive Predictive Value = {15/(15+97)}=13.39%
Negative Predictive Value = {35/(35+3)}=92.11%
Diagnostic Accuracy = 33.33%

**Validation of raised Alvarado score as a test for diagnosing cases of perforation plus impending perforation (gangrene)**

**Table-20: Validation of raised Alvarado score as a test for diagnosing cases of perforation plus impending perforation (gangrene)**

| Above average Alvarado score | Perforation or gangrene | others |
|---|---|---|
| yes | 39 | 73 |
| no | 3 | 35 |

Sensitivity = {39/(39+3)}= 92.86%
Specificity = {35/(35+73)}=32.41%
Positive Predictive Value = {39/(39+73)}= 34.82%
Negative Predictive Value = {35/(35+3)}=92.11%
Diagnostic Accuracy = 49.33%

**Association of each of the individual criteria of Alvarado score with the various groups**

**Table-21: Association of the individual criteria of Alvarado score with the various groups**

| Specific criterion in Alvarado score | Perforated group (N=18) | Gangrenous (N=24) | Simple (N=99) | Lump (N=6) | Abscess (N=3) |
|---|---|---|---|---|---|
| M | 12 | 15 | 32 | 3 | 1 |
| A | 12 | 21 | 83 | 6 | 3 |
| N | 18 | 24 | 88 | 6 | 3 |
| T | 18 | 24 | 93 | 6 | 3 |
| R | 18 | 15 | 21 | 0 | 1 |
| E | 18 | 24 | 81 | 6 | 3 |
| L | 9 | 18 | 8 | 0 | 0 |
| S | 12 | 15 | 6 | 0 | 0 |

M-Migratory pain, A-Anorexia, N-Nausea, T-Tenderness, R-Rebound Tenderness, E-Elevated temperature, L-Leukocytosis, S-Shift to the Left

**Leukocytosis**

Leukocytosis was present in only 35 (23.33%) patients in all. 135 (76.67%) patients had normal or low leukocytes. A greater proportion of perforation (9 out of 18 that is, 50%) and gangrene (18 out of 24 that is, 75%) patients had leukocytosis compared to simple appendicitis (8 out of 99 that is, only 8.08%). In fact, some patients had shift to the left but leukocytosis had not yet been established in them.

**Table-22: Descriptive statistics of leukocytosis in the various groups.**

| Group | Leukocytosis | No leukocytosis |
|---|---|---|
| Simple (catarrhal + suppurative) | 8(8.08%) | 91(91.92%) |
| gangrene | 18(75%) | 6(25%) |
| perforation | 9(50%) | 9(50%) |
| lump | 0 | 6(100%) |
| abscess | 0 | 3(100%) |
| Total | 35(23.33%) | 115(76.67%) |

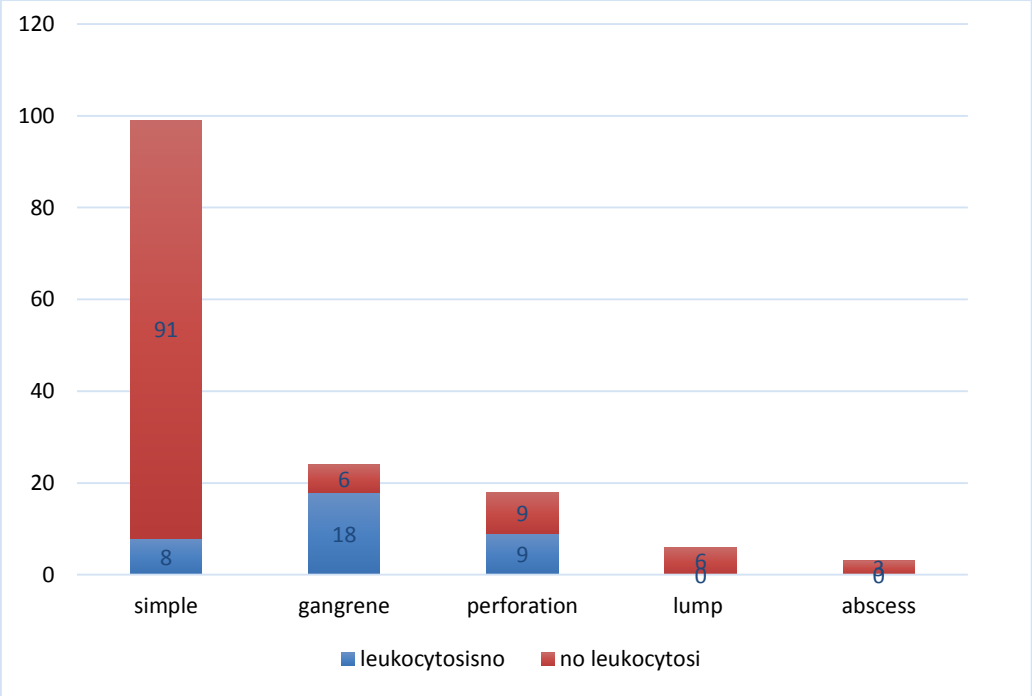


**Fig-10: Analysis of leukocytosis in the various groups**

**Validation of leukocytosis as a test to diagnose appendicular perforation**

**Table-23: Validation of leukocytosis as a test to diagnose appendicular perforation**

| Leukocytosis | Perforation present | Perforation absent |
|---|---|---|
| Yes | 9 | 26 |
| No | 9 | 106 |

Sensitivity = {9/(9+9)}= 50%
Specificity = {106/(106+26)}=80.3%
Positive Predictive Value = {9/(9+26)} = 25.71%
Negative Predictive Value = {106/(106+9)} = 92.17%
Diagnostic Accuracy = 76.67%

**Validation of leukocytosis as a test to diagnose perforation plus impending perforation (gangrene)**

**Table-24: Validation of leukocytosis as a test to diagnose perforation plus impending perforation (gangrene)**

| Leukocytosis | Perforation or gangrene | others |
|---|---|---|
| Yes | 27 | 8 |
| No | 15 | 100 |

Sensitivity = {27/(27+15)}= 64.29%
Specificity = {100/(100+8)}= 92.59%
Positive Predictive Value = {27/(27+8)} = 77.14%
Negative Predictive Value = {100/(100+8)}= 86.96%
Diagnostic Accuracy = 84.67%

**Association of hyperbilirubinemia raised CRP levels, above average Alvarado scores and leukocytosis in patients of various groups**

Out of the 18 patients with perforation 12(66.67%) each had raised bilirubin and CRP levels whereas 15(83.33%) had a raised Alvarado score and only 9(50%) had leukocytosis. All the 24 patients with gangrene had raised CRP levels and Alvarado score. But none had hyperbilirubinemia. Maximum patients with simple appendicitis (69 out of 99) had a significant Alvarado score, other parameters remaining, by and large, normal.

**Table-25: Association of hyperbilirubinemia raised CRP levels, above average Alvarado scores and leukocytosis in patients of various groups**

| Group | Number of patients | Hyperbilirubinemia | Raised CRP level | Raised Alvarado score | Leukocytosis |
|---|---|---|---|---|---|
| simple | 99 | 6 | 24 | 69 | 8 |
| gangrene | 24 | 0 | 24 | 24 | 18 |
| perforation | 18 | 12 | 12 | 15 | 9 |
| lump | 6 | 0 | 3 | 3 | 0 |
| abscess | 3 | 0 | 3 | 1 | 0 |

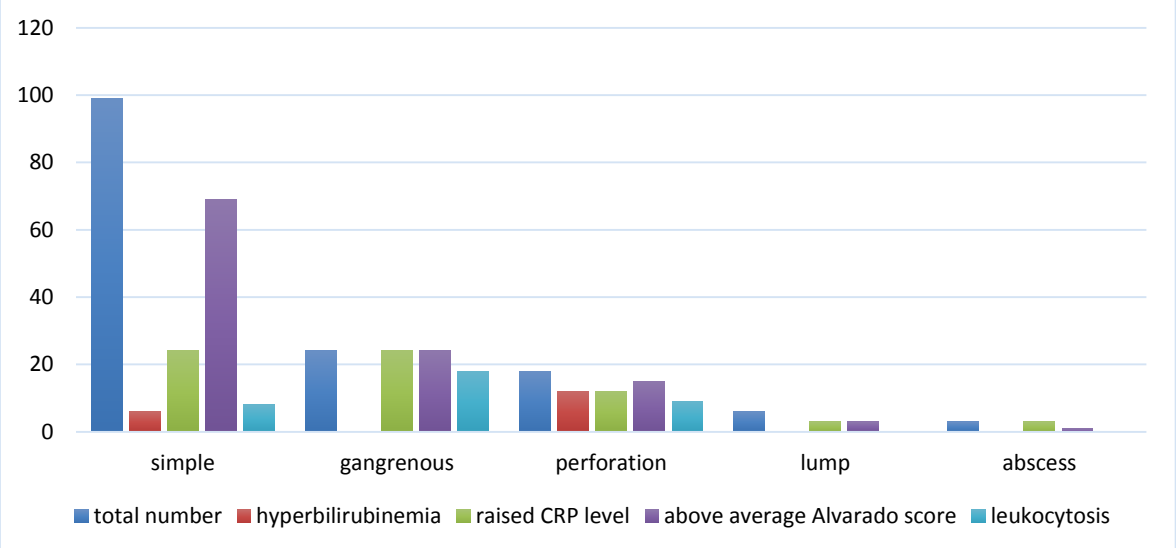


**Fig-11: Association of hyperbilirubinemia raised CRP levels, above average Alvarado scores and leukocytosis in patients of various groups**

**Comparison of the statistical parameters obtained for hyperbilirubinemia, raised CRP levels Alvarado score and leukocytosis as tests of diagnosis of appendicular perforation**

Hyperbilirubinemia had the highest sensitivity (66.67%), specificity (95.45%), positive predictive value (66.67%), negative predictive value (95.45%) and diagnostic accuracy (92%).

**Table-26: Comparison of the statistical parameters obtained for hyperbilirubinemia, raised CRP levels Alvarado score and leukocytosis as tests of diagnosis of appendicular perforation**

| Parameters | Hyperbilirubinemia (%) | Elevated CRP level (%) | Above average Alvarado score (%) | Leucocytosis (%) |
|---|---|---|---|---|
| Sensitivity | 66.67 | 66.67 | 83.33 | 50 |
| Specificity | 95.45 | 61.36 | 26.52 | 80.3 |
| Positive Predictive Value | 66.67 | 19.05 | 13.39 | 25.71 |
| Negative Predictive Value | 95.45 | 93.10 | 92.11 | 92.17 |
| Diagnostic Accuracy | 92 | 62 | 33.33 | 76.67 |

**Comparison of the statistical parameters obtained for hyperbilirubinemia, raised CRP levels Alvarado score and leukocytosis as tests to diagnose perforation plus impending perforation (gangrene)**

Alvarado score has highest sensitivity (92.86%), hyperbilirubinemia has highest specificity (94.44%), leukocytosis has highest positive predictive value (77.14%) and diagnostic accuracy and serum CRP level has the highest negative predictive value (93.1%).

**Table-27: Comparison of the statistical parameters obtained for hyperbilirubinemia, raised CRP levels Alvarado score and leukocytosis as tests to diagnose perforation plus impending perforation (gangrene)**

| Parameters | Hyperbilirubinemia (%) | Elevated CRP level (%) | Above average Alvarado score (%) | Leukocytosis (%) |
|---|---|---|---|---|
| Sensitivity | 28.57 | 85.71 | 92.86 | 64.29 |
| Specificity | 94.44 | 75 | 32.41 | 92.59 |
| Positive Predictive Value | 66.67 | 57.14 | 34.82 | 77.14 |
| Negative Predictive Value | 77.27 | 93.1 | 92.11 | 86.96 |
| Diagnostic Accuracy | 76 | 78 | 49.33 | 84.67 |

**Comparison between parameters for different tests for a) diagnosis of patients with perforation and b) diagnosis of patients with perforation plus those with impending perforation (gangrene)**

**Table-28: Comparison between parameters for different tests for a) diagnosis of patients with perforation and b) diagnosis of patients with perforation plus those with impending perforation (gangrene)**

| Parameters | Hyperbilirubinemia (%) | | Elevated CRP level (%) | | Above average Alvarado score (%) | | Leukocytosis (%) | |
|---|---|---|---|---|---|---|---|---|
| | a | b | a | b | a | b | a | b |
| Sensitivity | 66.67 | 28.57 | 66.67 | 85.71 | 83.33 | 92.86 | 50 | 64.29 |
| Specificity | 95.45 | 94.44 | 61.36 | 75 | 26.52 | 32.41 | 80.3 | 92.59 |
| Positive Predictive Value | 66.67 | 66.67 | 19.05 | 57.14 | 13.39 | 34.82 | 25.71 | 77.14 |
| Negative Predictive Value | 95.45 | 77.27 | 93.10 | 93.1 | 92.11 | 92.11 | 92.17 | 86.96 |
| Diagnostic Accuracy | 92 | 76 | 62 | 78 | 33.33 | 49.33 | 76.67 | 84.67 |

## DISCUSSIONS

In this study, we set out to find a clinicopathological correlation of hyperbilirubinemia as a predictor of perforation in acute appendicitis. At the very outset, we found that perforation occurred in 12% patients and another 16% had gangrene which is close to *Addiss et al* according to whom the perforation rate is 19.2 % [14]

In our study the female: male ratio came out to be 3:2 overall, but perforation occurred 5 times more commonly in males and gangrene 3 times more commonly in males. In the west, however, appendicitis in all its forms is more common in males [14].

According to literature the peak incidence is between 10 and 30 years with propensity towards complications in older age groups [14]. We also found the mean age in both the simple and gangrenous appendicitis groups to be less than 30 years, whereas perforation, lumps and abscesses were more common in older age groups.

Several studies found out that average duration of pain was 22 hours for non-perforated cases and 57 hours for perforated cases but some cases of perforation presented within 24 hours also [15]. We did not find significant difference in the duration of symptoms in patients with simple and perforated appendicitis. However, cases with gangrene presented later and it may be presumed that gangrene occurred due to delay in presentation [25]. The clinical features of perforation being more severe, patients probably presented earlier. In our hospital lumps and abscesses presented very late and were mostly referred from other facilities after preliminary conservative management. So, quite fallaciously, lumps and abscesses were seen to have milder derangements of clinical and biochemical parameters [26].

Various studies have advocated hyperbilirubinemia, raised CRP levels, WBC counts to be effective indicators of perforation [16-24, 27, 28]. Some studies postulated that CRP does better to differentiate between perforated and non-perforated cases [18, 20, 24]. *Sand M.* Bechara *et al* [27] found specificity of hyperbilirubinemia, CRP levels and WBC counts to be 85%, 35%, 55% respectively and sensitivity to be 70%, 81% and 96% respectively. According to another study the odds of appendicular perforation are three times higher for patients with hyperbilirubinemia compared to those with normal bilirubin levels [28]. Another study however stated that 86.6% of patients with acute appendicitis had hyperbilirubinemia which would make hyperbilirubinemia useless to differentiate between perforated and non-perforated appendicitis [29].

In our study we found statistical difference of mean and median bilirubin levels among the various groups, with patients having perforation having mean and median bilirubin levels > 1g/dl. All others had mean and median bilirubin levels within physiological limits, though for the gangrene group the mean and median were higher than simple appendicitis group.

Hyperbilirubinemia had sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of 66.67%, 95.45%, 66.67%, 95.45% and 92 % respectively when used to diagnose established perforation. But when it was used to predict both perforation or impending perforation the sensitivity decreased to 28.57%. Specificity almost remained unchanged at 94.44%, positive predictive value (ppv) remained same. However negative predictive value (npv) and diagnostic accuracy also dropped to 77.27% and 76% respectively.

Raised CRP levels had sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of 66.67%, 61.36%, 19.05%,93.10% and 62% when used to diagnose established perforation. But when it was used to predict both perforation or impending perforation the sensitivity, specificity, ppv and diagnostic accuracy all increased manifold to 85.71%, 75%, 57.14% and 78% respectively with npv remaining unaltered.

Above average Alvarado score (>=6) had sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of 83.33%, 26.52%, 13.39%, 92.11% and 33.33% respectively when used to diagnose established perforation. But when it was used to predict both perforation or impending perforation the sensitivity, specificity, ppv, npv and diagnostic accuracy became 92.86%, 32.41%, 34.82%, 92.11 % and 49.33% respectively.

When leukocytosis was used alone to diagnose established perforation, sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy were 50%, 80.3%, 25.71%, 92.17% and 76.67% respectively whereas, when it was used to predict both perforation or impending perforation the sensitivity, specificity, ppv, npv and diagnostic accuracy became 64.29%, 92.59%, 77.14%, 86.96% and 84.67% respectively.

Another pertinent question that could be raised is, why some cases have hyperbilirubinemia while some other cases of same severity do not. The cytokine and sepsis theories fail to explain this. However, the E. coli endotoxin theory could give a plausible explanation.

In our study, we found out a statistically significant correlation between detection of E. coli in abdominal fluid/pus culture and presence of hyperbilirubinemia.

## CONCLUSION

In this study we aimed to study the clinicopathological correlation of hyperbilirubinemia as a predictor of perforation in acute appendicitis. Except for lumps and abscesses patients had emergency appendectomy. The intraoperative findings were noted, specimens were sent for histopathology and pus/abdominal fluid samples were sent for culture. Now, on the basis of intraoperative and biopsy findings cases were classified into five groups- simple, gangrenous, perforated, lump and abscess. The bilirubin levels, CRP levels, Alvarado score and leukocyte counts of each group were studied. Sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy were calculated once as tests to diagnose established perforation and once as tests to detect impending (gangrene) plus established perforation.

To the clinician positive predictive value and diagnostic accuracy are most important. So, hyperbilirubinemia has a clear edge over the others when used to diagnose established perforation. In this

scenario, leukocytosis has high diagnostic accuracy but low positive predictive value. But, when used to diagnose cases with established perforation plus impending perforation i.e., gangrene the positive predictive value of CRP-test shoots up. But it still remains lower than that of leukocytosis and hyperbilirubinemia and in that order. However, its diagnostic accuracy surpasses that of bilirubin levels and comes second only to leukocytosis. High specificity of hyperbilirubinemia and leukocytosis in diagnosing established perforation as well as perforation or impending perforations taken together, implies that the absence of hyperbilirubinemia and leukocytosis virtually rules out the presence of perforation/impending perforation. Also a statistically significant Chi-square association was found between detection of E. coli in culture of abdominal fluid/pus and presence of hyperbilirubinemia.

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