Diagnostic Value of Total Leucocyte Count (TLC), C-reactive Protein (CRP) and Bilirubin in Patients with Suspected Acute Appendicitis

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ABSTRACT

Introduction: Total leukocyte count (TLC), C-reactive protein (CRP) and more recently, bilirubin have been used as adjuncts for diagnosis of appendicitis. This study assessed the diagnostic value of these markers in patients with suspected acute appendicitis.

Material and methods: The levels of TLC, CRP and bilirubin done within 24 hours of surgery were compared among the three groups of patients (1) normal appendix (NA), (2) acute appendicitis (AA) and (3) perforated appendicitis (PA). The diagnostic value of these markers was predicted for the above groups in terms of Sensitivity, specificity, PPVs and NPVs using sensitivity analysis and the diagnostic accuracy assessed by receiver operating characteristic (ROC) curve analysis.

Results: At the cut-off values: TLC 9000/mm^3, CRP 6 mg/L, total bilirubin 1.5 mmol/L, TLC had specificity (83.54%) for AA and a sensitivity and specificity of 100.0% and 83.54% respectively for PA. CRP was 94.68% sensitive to detect AA but less specific for both AA and PA (30.38%). Total bilirubin had a high sensitivity of 77.50% for PA. A combination of TLC and CRP had high sensitivity (96.25%) and specificity (83.54%) to detect PA. The specificity for PA increased (89.87%) with combination of all three tests.

Conclusion: TLC, CPR and Bilirubin can be helpful in the diagnosis and decision-making of patients with suspected appendicitis. A combination of TLC (≥9000/mm^3) and CRP (≥6 mg/L) had high sensitivity (96.25%) and specificity (83.54%) to detect PA. The specificity to detect PA increased (89.87%) when bilirubin (≥1.5 mmol/L) was also added to the above combination of markers.

Key words: Appendicitis, Bilirubin, C-reactive protein, Normal Appendix, Perforated appendicitis,, Total leucocyte count

INTRODUCTION

The diagnosis of appendicitis remains essentially clinical, requiring a mixture of observation, clinical acumen and surgical science. Despite appendicitis being a common disease, its presentation is not always typical and misdiagnosis is therefore not uncommon.[1] Diagnostic difficulties may lead to negative appendicectomies[2] or cases of missed appendicitis resulting in complications such as appendiceal perforation (AP) or abscess formation.[3]

Diagnostic scoring systems have been developed in an attempt to improve the diagnostic accuracy of acute appendicitis(AA).[4,5] The most prominent of these scores, developed by Alvarado,[5] gives points for symptoms (migration of pain, anorexia, and nausea), physical signs (right lower quadrant tenderness, rebound tenderness, and pyrexia), and laboratory values (leukocytosis and left shift). Although these scores can help guide clinical thinking, they do not markedly improve diagnostic accuracy.[6] Other diagnostic aids including ultrasound(USG), computed tomography(CT)[7] or even magnetic resonance imaging [MRI]),[8] do exist in order to help confirm the diagnosis or to guide the surgeon's decision on operative management or a period of observation when appendicitis is suspected.[9] However, these diagnostic adjuncts may be expensive, may involve high radiation exposure, and may not always have accurate and reproducible results.[9]

The diagnostic and discriminatory role of white cell count (WCC) and C-reactive protein (CRP) in AA has been studied expansively but still remains contentious.[10–14] Literature points that a rise in serum bilirubin level in patients with clinically suspected appendicitis may be a predictor for perforation of appendix.[15–20] It is well established that when microbes invade the body, leukocytes defend it. This leads to increase in the leukocyte count. Bacterial invasion in the appendix leads to transmigration of bacteria and the release of pro-inflammatory cytokines such as TNF-alpha, IL6 and cytokines. These reach the liver via Superior mesenteric vein (SMV) and may produce inflammation, abscess or dysfunction of liver either directly or indirectly by altering the hepatic blood flow.[21]

In view of the above context, the present study was undertaken to determine the diagnostic accuracy of WCC, CRP and bilirubin, either individually or when combined, in the prediction of appendicitis and, especially, its complications (i.e. perforated appendicitis [PA]).

MATERIAL AND METHODS

The approval was obtained from ethics Committee and signed informed consent were obtained from the patients. Based on the selection criteria, patients admitted with clinical suspicion of acute appendicitis under Department of Surgery, SMHS Hospital, Srinagar during the study period were screened for eligibility.

This prospective observational study was conducted in Shri Maharaja Hari Singh Hospital, a tertiary care hospital in the state of Jammu and Kashmir, catering a population of around 68.9 lakhs. Patients of all ages and either sex scheduled for emergency appendectomy between 1st May 2014 and 30 April 2015 were recruited for the study. Exclusion criteria included:

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1. Patients with past history of jaundice or liver disease.
2. Chronic alcoholism (intake of alcohol of > 40 g/day for men and > 20 g/day for women for 10 years).
3. Hemolytic disease.
4. Acquired or congenital biliary disease.
5. Patients with positive HBsAg.
6. Patients with cholelithiasis.
7. Patients with cancer of hepatobiliary system.
8. Patients known to be on treatment for any collagen vascular disease.
9. The appendectomy was performed as part of another procedure.

All enrolled patients were thoroughly evaluated for a detailed history, thorough general physical examination and systemic examination. The following investigations were done for all patients in the central investigation laboratory of the institutes within 24 hours prior to surgical intervention: (1) complete urine analysis (2) complete blood count (3) liver function tests (4) random blood sugar (5) blood urea and serum creatinine (6) Serum C-reactive protein (CRP) levels (7) serum electrolytes (Na^+ and K^+) (8) Hepatitis (B and C) and HIV serology (9) Coagulogram (Prothrombin time and International Normalized Ratio) (10) X-ray chest Postero-anterior view (11) Electrocardiogram and (12) Ultrasound abdomen.

Emergency appendectomy was conducted in all recruited patients through a formal grid iron or right lower paramedian incision. Intra-operative findings (perforation of appendix, presence of fluid and its character, intraluminal contents of appendix, appendicular base) were noted. The specimen was sent to the department of Pathology of the institute for histopathological examination. The results of the histopathological examination were recorded. On the basis of intraoperative findings and histopathological examination patients were classified as having a normal appendix (NA), acute appendicitis (AA) or perforated appendicitis (PA).

STATISTICAL ANALYSIS

Normal levels for the markers were: Total Leucocyte Count (TLC) 4–11 x 10^9 cells/L, CRP<10mg/L, bilirubin <21µmol/L. The levels of the above markers were summarized as mean and standard deviation. One-way analysis of variance followed by post-hoc comparison (Games-Howell) was used to compare the levels of markers (TLC, CRP, and bilirubin) among the three groups (NA, AA and PA).

The diagnostic value of TLC, CRP and bilirubin was predicted with sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for the above groups either for each individual test or when combined. Sensitivity, specificity, PPVs and NPVs varied when different cut-off values were examined (sensitivity analysis). The cut-off value finally chosen to compare sensitivity, specificity, PPV and NPV for each variable when looked at individually corresponded to the highest combined value for sensitivity and specificity, which resulted in a value either higher than normal or within the upper range of normal for each of the corresponding markers. Finally, the diagnostic accuracy of TLC, CRP and bilirubin was assessed by receiver operating characteristic (ROC) curve analysis. A p-value of <0.05 was considered statistically significant. SPSS version 20.0 was used for analysis of data.

RESULTS

A total of 615 eligible patients were enrolled during the study period. The mean age of patients was 23.94 ±7.476 years (range, 12–49 years) and the male: female ratio was 1.41. Two hundred seventy four patients (44.6%) had TLC above 11000/mm^3, and the differential leucocyte count showed predominance of neutrophils with mean neutrophil% of 80.84±6.94. Histopathological examination was done in all 615 patients. Based on histopathology and intra-operative findings acute AA was diagnosed in 376 (61.1%) patients and PA in 160 (26.0%) patients. Seventy nine (12.9%) patients did not have any evidence of appendicular perforation or inflammation. The clinical and laboratory findings of the patients are presented in Table 1. As compared to those with a normal appendix patients with any appendicitis were older, mostly males and had higher TLC and CRP levels. Patients with PA had higher total bilirubin levels as compared to patients with AA (P<0.001) or a normal appendix (P<0.001).

The next part of the analysis related to choosing cut-off values for calculating sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of TLC, CRP and total bilirubin for diagnosis of appendicitis. This was done by doing sensitivity analysis. The value with highest value of sensitivity and specificity was finally chosen as the cut-off. Table 2 shows the area under ROC curve for TLC, CRP and total bilirubin in AA and PA. The area under curve was highest for TLC and lowest for total bilirubin. Figure 1a and 1b depict the ROC curve for AA and PA respectively. The following cut-off values were taken for analysis: TLC 9000/mm^3, CRP 6 mg/L, total bilirubin 1.5 mmol/L.

Table 3 presents the diagnostic performance of TLC, CRP and total bilirubin individually and in combination for AA and PA. TLC had a high specificity (83.54%) to detect AA and a high sensitivity (100.0%) and specificity (83.54%) to detect PA. CRP had a high sensitivity to detect AA (94.68%) but a low specificity for both AA and PA (30.38%). Total bilirubin had a high sensitivity to detect PA (77.50%). A combination of TLC and CRP had high sensitivity (96.25%) and specificity (83.54%) to detect PA. The specificity to detect PA increased (89.87%) when a combination of all three tests was used.

DISCUSSION

Acute Appendicitis (AA), an inflammation of the vestigial vermiform appendix, is one of the most common reasons for acute abdomen and for emergent surgery. A constellation of history, physical signs, radiographic investigation, and laboratory analysis is used to diagnose an acute appendicitis. The most important step in the management of patients with suspected appendicitis is reaching the decision about operative intervention and its timing so that both negative appendicectomies and complicated appendicitis rates are kept to a minimum.

In this observational study, 615 patients were prospectively recruited over a period of one year. The negative appendicectomy rate in our study was 12.8% whereas that of PA

	Normal Appendix (n=79)	Acute Appendicitis (n=376)	Perforated Appendicitis (n=160)	Total (n=615)	p value
Age (Mean, S.D.)	20.49, 4.359	23.76, 7.355	26.06, 8.271	23.94, 7.476	<0.001[A], <0.001[B], 0.007[C]
Sex(Male:Female)	37:42	216:160	107:53	360:255	0.010
TLC (Mean, S.D.)	6.868, 1.8134	10.305, 2.3678	12.801, 2.3588	10.513, 2.8952	<0.001[A], <0.001[B], <0.001[C]
CRP (Mean, S.D.)	5.65, 0.578	9.66, 4.104	11.85, 6.085	9.72, 4.820	<0.001[A], <0.001[B], <0.001[C]
Bilirubin (Mean, S.D.)	1.384, 0.9364	1.466, 0.3860	2.349, 0.8856	1.685, 0.7494	0.725[A], <0.001[B], <0.001[C]

[A]Normal Appendix versus Acute Appendicitis, [B]Normal Appendix versus Perforated Appendicitis, [C]Acute Appendicitis versus Perforated Appendicitis

Table-1: The clinical and laboratory findings of 615 patients.

	ROC Area Under Curve (95% CI)	
	Acute appendicitis(AA)	Perforated appendicitis(PA)
TLC	0.866 (0.824, 0.907)	0.995 (0.989, >0.999)
CRP	0.816 (0.775, 0.857)	0.830 (0.780, 0.879)
Bilirubin	0.608 (0.540, 0.676)	0.779 (0.715, 0.843)

Table-2: Shows the area under ROC curve for TLC, CRP and total bilirubin in AA and PA.

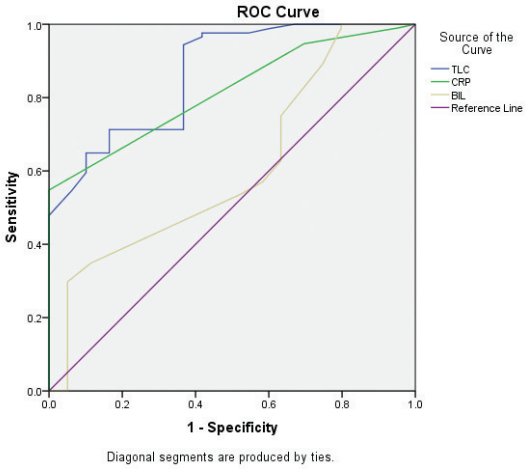

Figure-1: Receiver operating characteristic curves for white cell count (WCC), C-reactive protein (CRP) and bilirubin in predicting acute appendicitis. AUC value provided with 95% confidence interval in parentheses.

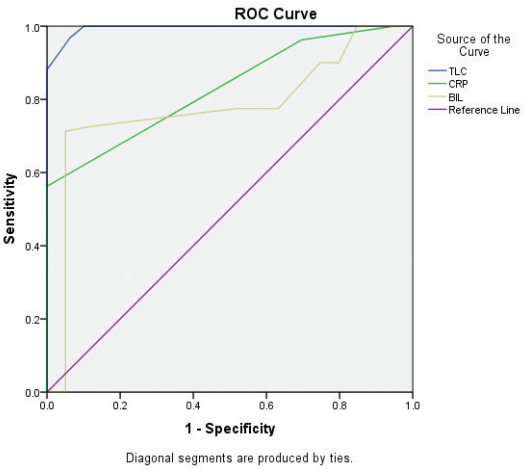

Figure-2: Receiver operating characteristic curves for white cell count (WCC), C-reactive protein (CRP) and bilirubin(bil) in predicting perforated appendicitis. AUC value provided with 95% confidence interval in parentheses.

was 26.0%. Previous studies have reported negative appendicectomy rates of up to 20% in male and 30% in female patients.[22,23] In our case series, the negative appendicectomy rate was lower because all patients who had a diagnostic quandary were subjected to diagnostic laparoscopy and were excluded from the study. A great variation exists in the rate of PA in the literature, with PA percentage ranging from 3.5% to 25%.[24-26]

Till now there is no confirmatory laboratory marker for the pre-operative diagnosis of acute appendicitis and appendicular perforation. To supplement the clinical diagnosis and to reduce the frequency of unnecessary appendicectomy, the importance of laboratory investigations like White Blood Cell (WBC) counts and C-reactive protein (CRP) values has been stressed.[27] Recently, elevation in serum bilirubin was reported, but the importance of the raised total bilirubin has not been stressed in appendicitis.[28] In our study, when considered in isolation, TLC was found to be a sensitive and specific tool for diagnosis of AA and PA. Bilirubin, in isolation, was found to have moderate sensitivity for PA.

In a meta-analysis, Andersson concluded that most diagnostic information comes from a history of migratory pain, clinical assessment confirming peritoneal irritation and inflammatory markers.[29] He also suggested that inflammatory variables in advanced appendicitis appear to be at least as important discriminators as the clinical descriptors of peritoneal irritation.

In this study we investigated the value of TLC, CRP and total Bilirubin in patients with suspicious signs of appendicitis and correlated the values with the intra-operative findings and histopathological examination of the specimens. TLC was found to have high sensitivity and specificity for PA. A TLC of $<9x10^3$ cells/L was found to rule out PA but not AA. CRP≥6 mg/L was found to have high sensitivity for diagnosis of both AA and PA, but had a very low specificity (30.38%). Increased levels of both TLC ($\geq 9x10^3$ cells/L) and CRP (≥6 mg/L) almost confirm a diagnosis of appendicitis (PPV=94.84% for AA and 92.22% for PA). Normal levels of both TLC and CRP rule out a diagnosis of PA but do not necessarily rule out AA. This is in contrast to the findings of Sengupta A[30] et al, who have suggested that normal TLC with normal CRP levels decrease the possibility of AA and that the patient can be discharged without more reviews. Riazi[31] et al reports that the possibility of negative appendectomy in patients with both positive tests has been less than 10.0%.

In our study mean bilirubin level was highest among patients

		Sensitivity(95%CI)	Specificity (95%CI)	PPV(95%CI)	NPV(95%CI)	Diagnostic accuracy(95%CI)
TLC. (cut off = 9×10^3 cells/l)	AA	66.76%(61.85,71.33)	83.54%(73.85,90.12)	95.08%(91.76,97.1)	34.55%(28.18,41.54)	69.67%(65.3,73.1
	PA	100%(97.66,100)	83.54%(73.85,90.12)	92.49%(87.57,95.56)	100%(94.50,100)	94.56%(90.92,96.79)
CRP (cut off= 6 mg/l)	AA	94.68(91.93,96.53)	30.38%(21.34,41.23)	86.62%(82.99,89.57)	54.55%(40.07,68.29)	83.52%(79.83,86.64)
	PA	96.25%(92.06,98.27)	30.38%(21.34,41.23)	73.68%(67.33,79.19)	80.00%(62.69,90.50)	74.48%(68.59,79.59)
Bilirubin (cut off = 1.5 mmol/l)	AA	53.46%(48.41,58.44)	48.10%(37.43,58.95)	83.06%(77.82,87.26)	17.84%(13.28,23.54)	52.53%(47.94,57.08)
	PA	77.50%(70.43,83.28)	48.10%(37.43,58.95)	75.15%(68.04,81.12)	51.35%(40.18,62.39)	67.78%(61.62,73.39)
TLC/CRP	AA	63.56%(58.58,63.27)	83.54%(73.85,90.12)	94.84%(91.38,96.96)	32.51%(26.45,39.23)	67.03%(62.59,71.19)
	PA	96.25%(92.06,98.27)	83.54%(73.85,90.12)	92.22%(87.14,95.39)	91.67%(82.99,96.12)	92.05%(87.92,94.85)
TLC/CRP/Bilirubin	AA	36.97%(32.24,41.96)	89.87%(81.27,94.78)	94.56%(89.63,97.22)	23.05%(18.70,28.07)	46.15%(41.62,50.75)
	PA	73.75%(66.43,79.95)	89.87%(81.27,94.78)	93.65%(87.97,96.75)	62.83%(53.64,71.18)	79.08%(73.48,83.76)

Table-3: Sensitivity, specificity, positive predictive values (PPV) and negative predictive values (NPV) for white cell count (WCC), C-reactive protein (CRP) and bilirubin in all 615 patients when predicting acute appendicitis (AA) or perforated appendicitis (PA).

with PA. This observation is supported by Dipen Patel[24] et al who found that the mean bilirubin levels in patients diagnosed with complicated appendicitis were higher as compared to that in patients with acute uncomplicated appendicitis. Potential mechanisms that result in hyperbilirubinaemia in appendicitis could be either due to increased haemolysis by E coli and therefore increased bilirubin load[32] or due to endotoxin induced cholestasis.[33] Several studies have suggested that patients with clinical appendicitis and hyperbilirubinaemia are more likely to have appendiceal perforation.[15–20] An increased bilirubin level (≥1.5 mmol/L) was found to have high sensitivity and high PPV for detecting PA in our study. However it did not play any major role as an adjunct to increased TLC and CRP.

TLC and CRP are non-specific inflammatory mediators. A pre-disease TLC and CRP status of patients in our study was not known, which otherwise would have helped in making a better decision regarding increased reason for increased levels of these mediators. Furthermore, levels of direct and indirect bilirubin were not separately known. Such information would have helped in a more specific analysis.

CONCLUSIONS

The results of this study showed that in addition to history and physical examination, some basic laboratory findings such as TLC, CPR and Bilirubin can be helpful in the diagnosis and decision making of patients with suspected appendicitis. A combination of TLC(≥9000/mm^3) and CRP(≥6 mg/L) had high sensitivity (96.25%) and specificity (83.54%) to detect PA. The specificity to detect PA increased (89.87) when total bilirubin(≥1.5 mmol/L) was also added to the above combination of markers.

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