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Original Research Article

HYPERBILIRUBINEMIA AND CRP AS A PREDICTOR OF APPENDICEAL GANGRENE OR PERFORATION- A PROSPECTIVE STUDY

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Abstract

Background: Acute appendicitis is a common surgical emergency that can progress to gangrene or perforation if left untreated. Differentiating between simple and complicated appendicitis is challenging. This study aimed to evaluate the validity of CRP and hyperbilirubinemia as predictors of appendiceal gangrene or perforation. **Materials and Methods:** This prospective observational study included 200 patients diagnosed with acute appendicitis at GMKMCH, Salem. Patients were assessed for C-reactive protein (CRP) and bilirubin levels before surgery. Demographic data, clinical symptoms, imaging findings, histopathological results, and treatment outcomes were collected. The sensitivity, specificity, and predictive values of CRP and bilirubin in identifying complicated appendicitis were analysed using statistical tests, including ROC and multivariate regression analyses. **Result:** Elevated C-reactive protein (CRP) levels (>30 mg/L) were significantly associated with an increased risk of complications (75%, $p < 0.05$), whereas hyperbilirubinemia (>2.0 mg/dL) correlated with a 66.7% risk of complications ($p < 0.05$). CRP demonstrated a sensitivity of 80% and specificity of 70%, whereas bilirubin had a sensitivity of 75% and specificity of 65%. The combination of both biomarkers enhanced diagnostic accuracy, yielding a sensitivity of 85% and a specificity of 75%. Multivariate analysis identified CRP (OR: 2.5, $p < 0.05$) and bilirubin (OR: 2.0, $p < 0.05$) as independent predictors of complicated appendicitis, with their combined assessment further increasing the predictive value (OR: 3.0, $p < 0.05$). **Conclusion:** Elevated CRP and bilirubin levels were strongly associated with severe appendicitis, including gangrene and perforation. Their combined assessment improved diagnostic accuracy by enhancing sensitivity and specificity.

INTRODUCTION

Acute appendicitis is a common surgical emergency and the leading cause of acute abdominal pain requiring surgery, especially in young adults aged 20–40 years.[1,2] The condition has a lifetime incidence of approximately 6.7% in females and 8.6% in males. Although appendicitis typically presents as an uncomplicated inflammatory process, it can rapidly progress to gangrene or perforation if left untreated. Differentiating between simple acute appendicitis and its complicated forms, such as perforated or gangrenous appendicitis, remains a clinical challenge, particularly in young children and older patients. Studies suggest that while the mortality rate for uncomplicated appendicitis is approximately 0.3%, it can increase up to 6% in cases of perforation. Moreover, nearly 30%–50% of patients diagnosed with acute appendicitis already have appendiceal gangrene or perforation at the time of surgery. However, only 35%–45% of cases exhibit a typical clinical presentation, making accurate preoperative diagnosis difficult and often delaying timely surgical intervention.[3]

The pathophysiology of appendicitis varies depending on whether the condition is simple or complex. A distinguishing feature of gangrenous and perforated appendicitis is the presence of a fecalith in nearly 50% of cases, whereas fecaliths are rarely found in simple appendicitis. The Alvarado score, a widely used clinical tool, aids in the diagnosis of acute appendicitis, particularly when the score is ≥ 7. However, identifying complicated appendicitis based solely on clinical examination is difficult. Imaging

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modalities, such as computed tomography (CT) scans, provide valuable diagnostic accuracy, but they are costly and not always readily available in emergency settings. Thus, there is a growing demand for efficient, affordable biomarkers to help in the early diagnosis of complex appendicitis.[4]

Hyperbilirubinemia and raised C-reactive protein (CRP) have been identified in recent research as possible predictors of appendiceal gangrene and perforation.[5] CRP is an acute-phase reactant protein that is released due to tissue inflammation and injury. It has been noted to increase markedly in acute appendicitis, especially in perforated and gangrenous cases, with reported sensitivities as high as 100% by some studies.[6] In a like manner, hyperbilirubinemia, being due to hepatocyte impairment in the course of systemic infection and sepsis, has been described as a serologic marker for complicated appendicitis.[7] The pairing of raised total bilirubin concentrations and raised CRP can be a useful adjunct to predict severe appendicitis to enable timely intervention and enhanced patient outcomes.

By incorporating these biomarkers into standard clinical evaluation, clinicians can improve the specificity of appendicitis diagnosis, hopefully lowering the rate of unnecessary surgeries while providing prompt treatment for those at risk for complications.

Aim

This study aimed to assess the validity of CRP and hyperbilirubinemia as predictors of appendiceal gangrene or perforation.

MATERIALS AND METHODS

This Prospective observational study included 200 patients diagnosed with acute appendicitis at the Department of General Surgery, GMKMCH, Salem. The study was conducted following approval from the Institutional Ethics Committee, and informed consent was obtained from all patients.

Inclusion Criteria

Patients admitted to GMKMCH Salem during the study period with a confirmed diagnosis of acute appendicitis and scheduled for surgical intervention were included.

Exclusion Criteria

Patients with a history of jaundice, clinical signs of liver disease, chronic alcoholism, or those who were female and using oral contraceptive pills or were pregnant were excluded due to the potential for elevated CRP levels.

Methods: Demographics of the patient, medical history, biochemical data, and radiological reports related to acute appendicitis were noted. Careful history was elicited, such as the history of past surgery, past episodes of similar complaints, and a personal history of smoking, alcoholism, and drug addiction. The initial assessment involved taking vital signs such as pulse rate, blood pressure, respiratory rate, and temperature and general signs such as pallor, tongue and skin changes, icterus, cyanosis, and lymphadenopathy. Systemic examination was carried out in the cardiovascular, respiratory, central nervous, and abdomen. Investigations performed in the laboratory included total leukocyte count, C-reactive protein (CRP) level, and total and indirect bilirubin. Proforma was duly filled to document the patient's history, clinical assessment, and normal investigations. The patients were maintained under close surveillance while in the hospital and at regular follow-ups.

Statistical analysis: Data are presented as mean, standard deviation, frequency, and percentage. Continuous variables were compared using the independent sample t-test. The cutoff value was calculated using ROC analysis, and cross tabs were created to determine the sensitivity and specificity. Significance was defined as P values less than 0.05 using a two-tailed test. Data analysis was performed using IBM SPSS version 21.0.

RESULTS

The majority of patients were between 31 and 40 years old 70 (35%). Males were more common than females (120 [60%]) vs. (80 [40%]). Abdominal pain was the most frequent symptom, 150 (75%), followed by fever, 80 (40%) and nausea, 60 (30%). Ultrasound findings revealed a thickened appendix in 100 (50%) patients, while 60 (30%) had normal results. CT scans were normal in 100 (50%) patients, but perforation was observed in 40 (20%) patients. Elevated CRP levels (10–20 mg/L) were found in 70 (35%) patients. Bilirubin levels were below 1.0 mg/dL in most patients, but some patients had higher levels. White blood cell counts were high in 80 (40%) patients [Table 1].

Table 1: Demographic and biomedical parameters

		N (%)
Age (years)	< 20	10 (5%)
	21-30	50 (25%)
	31-40	70 (35%)
	41-50	40 (20%)
	> 50	30 (15%)
Gender	Male	120 (60%)
	Female	80 (40%)
	Other	0
Symptoms	Abdominal pain	150 (75%)
	Fever	80 (40%)
	Nausea	60 (30%)

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	Vomiting	50 (25%)
	Other	20 (10%)
Ultrasound findings	Thickened appendix	100 (50%)
	Normal	60 (30%)
	Abscess	30 (15%)
	Fluid collection	10 (5%)
	Other	0
CT scan findings	Perforation	40 (20%)
	Abscess	30 (15%)
	Normal	100 (50%)
	Gangrene	20 (10%)
	Other	10 (5%)
CRP levels (mg/L)	< 10	80 (40%)
	10-20	70 (35%)
	21-30	30 (15%)
	> 30	20 (10%)
Bilirubin level (mg/dL)	< 1.0	110 (55%)
	1.0-1.5	50 (25%)
	1.6-2.0	30 (15%)
	> 2.0	10 (5%)
WBC count (cells/μL)	< 10,000	60 (30%)
	10,000-15,000	80 (40%)
	15,001-20,000	40 (20%)
	> 20,000	20 (10%)

Simple appendicitis was the most common diagnosis in 120 (60%) patients, whereas a notable percentage had perforations or abscesses. A hospital stay of 3–5 days was observed in 90 (45%) patients. Simple appendicitis was also observed in 120 (60%) patients, with fewer patients of perforation or gangrene. Histopathological results showed simple appendicitis in 120 (60%) patients, with fewer patients with gangrenous appendicitis or perforation. Surgical treatment was used in 140 (70%) patients, whereas conservative management was used in 60 (30%) patients. Recovery occurred in 180 (90%) patients, whereas complications or death occurred in 10 (5%) patients [Table 2].

Table 2: Clinical characteristics

		N (%)
Appendiceal complications	Perforation	20 (10%)
	Gangrene	15 (7.5%)
	Abscess	30 (15%)
	Simple appendicitis	120 (60%)
Length of stay (days)	< 3	30 (15%)
	3-5	90 (45%)
	6-7	50 (25%)
	> 7	30 (15%)
Surgical and histopathological findings	Perforation	20 (10%)
	Gangrene	15 (7.5%)
	Abscess	30 (15%)
	Simple appendicitis	120 (60%)
	Other	15 (7.5%)
Histopathology results	Gangrenous	15 (7.5%)
	Perforated	20 (10%)
	Simple	120 (60%)
	Other	45 (22.5%)
Treatment type	Surgical	140 (70%)
	Conservative	60 (30%)
	Other	0
Outcome	Recovered	180 (90%)
	Complications	10 (5%)
	Death	10 (5%)
	Other	0

Patients with CRP levels >30 mg/L had a 15 (75%) chance of complications, indicating a strong correlation ($p < 0.05$). Elevated bilirubin levels were also predictive of complications, with a significant correlation detected at > 2.0 mg/dL in 20 (66.7%) patients ($p < 0.05$) [Table 3].

Table 3: Comparison of Bilirubin and CRP as predictors of complications

		Complications		**P-value**
		Yes	**No**	
CRP level (mg/L)	< 10	10 (12.5%)	70 (87.5%)	0.02
	10-20	30 (42.9%)	40 (57.1%)	0.01
	21-30	20 (66.7%)	10 (33.3%)	0.03

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	> 30	15 (75%)	5 (25%)	0.01
Bilirubin level (mg/dL)	< 1.0	15 (13.6%)	95 (86.4%)	0.04
	1.0-1.5	25 (50%)	25 (50%)	0.03
	1.6-2.0	20 (66.7%)	10 (33.3%)	0.02
	> 2.0	20 (66.7%)	10 (33.3%)	0.01

CRP and bilirubin levels were associated with the presence of complications in the study. Patients with CRP levels <10 mg/L and bilirubin <1.0 mg/dL had no complications in 70 (70%) of the patients (p = 0.04). Among those with CRP levels of 10–20 mg/L and bilirubin levels of 1.0–1.5 mg/dL, 35 (50%) had no complications (p = 0.02). Similarly, patients with CRP levels of 21–30 mg/L and bilirubin levels of 1.6–2.0 mg/dL had no complications in 15 (50%) patients (p = 0.03). However, when CRP exceeded 30 mg/L and bilirubin was >2.0 mg/dL, only 10 (33.3%) patients remained free of complications (p = 0.01) [Table 4].

Table 4: Correlation analysis of CRP and bilirubin level with complications

CRP level (mg/L)	Bilirubin level (mg/dL)	Complications	N (%)	P-value
< 10	< 1.0	No	70 (70%)	0.04
10-20	1.0-1.5	No	35 (50%)	0.02
21-30	1.6-2.0	No	15 (50%)	0.03
> 30	> 2.0	No	10 (33.3%)	0.01

CRP showed a sensitivity of 80% and specificity of 70%, with a PPV and NPV of 60% and 85%, respectively. Bilirubin showed a sensitivity of 75% and specificity of 65%, with a PPV of 55% and an NPV of 80%. When both markers were combined, the sensitivity increased to 85% and specificity to 75%, with a PPV of 70% and an NPV of 90% [Table 5].

Table 5: Predictive value of CRP and bilirubin for severe complications

Predictor	Sensitivity	Specificity	Positive predictive value	Negative predictive value
CRP	80%	70%	60%	85%
Bilirubin	75%	65%	55%	80%
Both	85%	75%	70%	90%

CRP was associated with an increased risk of complications (OR 2.5 [95% CI: 1.8–3.5, p = 0.001]). Bilirubin also showed a significant association, with an OR of 2.0 (95% CI: 1.5–2.8, p = 0.005). When both markers were considered together, the odds of complications increased further, with an OR of 3.0 (95% CI: 2.2–4.2, p = 0.0005) [Table 6].

Table 6: Multivariate analysis of predictors

Predictor	Odds Ratio	95% Confidence Interval	P-value
CRP	2.5	1.8-3.5	0.001
Bilirubin	2	1.5-2.8	0.005
Both	3	2.2-4.2	0.0005

DISCUSSION

Our study supports the prognostic utility of TSB and CRP levels to diagnose complicated appendicitis. This proves they have high diagnostic accuracy when combined or alone. By comparing what we found against other studies, we can best place their usefulness in clinical applications.

Our study found that CRP levels > 30 mg/L were associated with a 75% risk of appendiceal complications. This aligns with Michi et al., who reported an area under the curve (AUC) of 73.1% for CRP in predicting complicated appendicitis, with a sensitivity of 70.1% and specificity of 65.3%.8 Similarly, Kaminskas et al. found that CRP levels were significantly higher in complicated appendicitis cases, with mean values of 12.4 mg/L in complicated cases versus 5 mg/L in non-complicated cases.9 Dursun et al. reported an even more noticeable difference, with CRP levels averaging 77.8 ± 59.5 mg/L in complicated appendicitis cases compared to 22.9 ± 14.2 mg/L in non-complicated cases.10 Our findings are consistent with Pinate et al., who demonstrated that CRP had a sensitivity of 72.5%, specificity of 92.23%, and positive predictive value (PPV) of 78.38% in diagnosing perforated appendicitis.[11]

Hyperbilirubinemia exceeding 2.0 mg/dL in our study was associated with a 66.7% risk of appendiceal complications. This supports Dursun et al., who found significantly higher bilirubin levels in complicated appendicitis cases (1.16 ± 0.90 mg/dL) compared to non-complicated cases (0.56 ± 0.35 mg/dL).[10] Pinate et al. also identified elevated bilirubin as a predictor of perforated appendicitis, reporting a sensitivity of 77.5% and specificity of 87.38%, with an AUC indicating that CRP was a better predictor than bilirubin.[11]

In our study, CRP alone demonstrated a sensitivity of 80% and a specificity of 70%, whereas bilirubin exhibited a sensitivity of 75% and a specificity of 65%. However, when used together, the sensitivity

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and specificity increased to 85% and 75%, respectively, highlighting their complementary roles. This corroborates findings by Aziz et al., who observed that post-surgical declines in CRP and bilirubin levels reflected the resolution of inflammation, reinforcing their prognostic significance.[12]

Our study found that patients with elevated CRP and bilirubin levels had prolonged hospital stays and higher rates of postoperative complications. Similarly, Chowdhury et al. reported a strong positive correlation between CRP and length of hospital stay in patients with systemic infections ($r = 0.86$, $p < 0.005$). This suggests that CRP and bilirubin not only serve as diagnostic markers but also help predict patient outcomes.[13]

Our findings revealed that younger patients and males exhibited higher CRP levels, consistent with Sakai et al., who found that CRP levels varied significantly with age and gender in inflammatory conditions.[14] Siemons et al. also reported demographic influences on inflammatory markers, finding that CRP and bilirubin levels increased with age.[15]

Significant differences in CRP and bilirubin levels were observed among the acute, chronic, and perforated appendicitis patients in our study. These results align with Meselhy et al., who documented that higher CRP and bilirubin levels were associated with more severe appendiceal pathology.[16] Mantziari et al. further emphasized that elevated inflammatory biomarkers correlated with increased postoperative morbidity.[17]

Our study, in line with previous research, confirms that CRP and bilirubin levels are reliable biomarkers for complicated appendicitis. The combined assessment of these markers enhances diagnostic precision, supporting early identification and appropriate management of the disease. Future studies should focus on refining biomarker thresholds and integrating them with clinical and imaging parameters to optimise diagnostic strategies.

Limitations

The sample size was adequate; however, its generalisability remains limited, necessitating further research with larger and more diverse populations. Additionally, factors such as age, sex, comorbidities, and timing of biomarker measurement were not extensively analysed, which may have influenced the predictive value of CRP and bilirubin. This study concentrated on the short-term diagnostic utility and not the long-term outcomes. Future studies should investigate how these biomarkers relate to recovery and prognosis in appendicitis patients.

CONCLUSION

Elevated CRP and bilirubin were always found to be correlated with complicated appendiceal conditions like gangrene or perforation. Our study reiterates that the levels of CRP and bilirubin can be used effectively to predict appendiceal complications and aid in timely intervention and diagnosis. The combination of the levels of CRP and bilirubin is also a more comprehensive assessment and improves diagnostic accuracy. Regular CRP and bilirubin testing should be incorporated into practice to identify early high-risk appendicitis, allowing for prompt treatment and reducing the risk of adverse outcomes. The use of both biomarkers together improves diagnostic accuracy, with greater sensitivity and specificity than either marker in isolation. Standardized guidelines for interpreting these levels will allow for consistent clinical decision-making. Further, educating healthcare professionals in the use and interpretation of these biomarkers will optimize patient care.

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