

Original Research Article

Role of C reactive protein, hyperbilirubinemia and mean platelet volume in diagnosis of acute appendicitis and its correlation post operatively with histo-pathological examination

Tiwari Sachin Mahendra, Saurabh Agrawal*

Department of General Surgery, Heritage Institute of Medical Sciences, Varanasi, Uttar Pradesh, India

Received: 09 May 2023

Revised: 07 June 2023

Accepted: 09 June 2023

*Correspondence:

Dr. Saurabh Agrawal,

E-mail: saurabhms005@yahoo.co.in

Copyright: © the author(s), publisher and licensee Medip Academy. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ABSTRACT

Background: Acute appendicitis is one of the most common abdominal emergencies requiring emergency surgery. The diagnosis based on the onset of symptoms and physical examination. Therefore, inaccuracies caused by subjective interpretation are frequent. This raises the need for tests to help diagnose acute appendicitis and predict the severity of the condition. aim of the study to investigate whether mean platelet volume, C-reactive protein, and hyperbilirubinemia can be used as inflammatory markers for the diagnosis of acute appendicitis and its correlation with histopathological examination.

Methods: we prospectively analyzed 60 patients who were full fulling the inclusion criteria patients analysed for CBC, LFT and CRP and underwent for appendectomy (Laparoscopic/open). Per-operative diagnosis was confirmed by histopathological examination from November 2020 to November 2022.

Results: patients with CRP level > 6 and hyperbilirubinemia patients most likely to have acute appendicitis. Mean CRP level was 13.21 ± 4.0 and mean bilirubin level 1.04 ± 0.29 in case of acute appendicitis. CRP, hyperbilirubinemia levels were significantly higher in cases of acute appendicitis ($p < 0.01$) while MPV value was not found significant. All patients was confirmed with histopathology examination.

Conclusions: Serum bilirubin level and CRP estimation, which is a simple, cheap, and easily available laboratory test, can be added to the routine investigations in the diagnosis and severity of acute appendicitis and help in decreasing negative appendectomy rates, especially in low modified Alvarado score.

Keywords: Acute appendicitis, CRP, Hyperbilirubinemia, Mean platelet volume

INTRODUCTION

Acute appendicitis is one of the most common abdominal emergencies requiring emergency surgery, and appendectomy is the most frequently performed emergency operation worldwide in general practice.¹

Doctors base the diagnosis of acute appendicitis on history and physical examination. As written in Bailey and Love, "Notwithstanding advances in modern radiographic imaging and diagnostic laboratory investigations, the diagnosis of appendicitis remains

essentially clinical, requiring a mixture of observation, clinical acumen, and surgical science."²

The cause of acute appendicitis is unknown and is likely to be multifactorial; luminal obstruction, and dietary and familial factors have been suggested as potential contributors to acute appendicitis.

A retrocecal or retro-ileal appendix is difficult to diagnose. Appendectomy is the most commonly performed abdominal surgery.

Delayed diagnosis and treatment of severe appendicitis are associated with an increased risk of perforation and postoperative morbidity, mortality, and hospital stay. There is an urgent need for a predictor of the severity of acute appendicitis, 15-30% of post-appendectomy specimens are found to be normal.

The importance of laboratory tests such as white blood cell count, C-reactive protein, mean platelet volume, and hyperbilirubinemia is emphasized to reduce the number of unnecessary appendectomies.

Gross abdominal USG is widely accepted as a diagnostic tool for acute appendicitis. Many scoring systems have been developed to facilitate diagnosis.

These grading systems are based on clinical characteristics and laboratory tests. Some examples are Alvarado, modified Alvarado, and RIPASA score. There are still no clear laboratory markers for the diagnosis of acute appendicitis.

Alvarado score was proposed for appendicitis based on clinical signs, physical examination, and laboratory data. Mean platelet volume is a measure of platelet size generated by blood count analysers as part of a routine complete blood count.

Elevated bilirubin occurs secondary to endotoxins released in the peripheral blood, which prevent the liver's mechanism of uptake of bilirubin and its excretion by the ducts. C-reactive protein is an acute-phase protein that many surgeons often rely on as a diagnostic marker for acute appendicitis.³

Bacterial invasion of the cecum leads to bacterial migration and release of pro-inflammatory cytokines such as TNF α and IL6. Cytokines enter the liver via the superior mesenteric vein and can cause inflammation, abscesses, and liver dysfunction.⁴

To investigate hyperbilirubinemia and acute appendicitis, evaluate its reliability as a diagnostic marker of acute appendicitis, and determine whether elevated bilirubin levels are predictive of a diagnosis of appendiceal perforation.

CRP is a non-specific inflammatory marker used for diagnosis in patients with acute abdomen. It is an acute-phase protein which produced in the liver. Evaluation of inflammatory markers is considered to be helpful in the diagnosis of acute appendicitis.⁵

The acute appendicitis diagnosis is based on the onset of symptoms and physical examination. Therefore, inaccuracies caused by subjective interpretation are frequent. This raises the need for tests to help diagnose acute appendicitis and predict the severity of the condition.

Because of the above context, the present study was undertaken to assess the relationship between C-reactive protein, hyperbilirubinemia, MPV, and acute appendicitis and to evaluate its credibility as a diagnostic marker for the diagnosis of acute appendicitis.

METHODS

We prospectively analyzed 60 patients from November 2020 to November 2022 in the department of general surgery, heritage institute of medical sciences, Varanasi.

Inclusion criteria includes 1. Age more than 16 years 2. All clinically diagnosed patients of acute appendicitis presenting to the OPD within 72 hours of symptoms and the exclusion criteria includes 1. Patients who presented 72 hours after the onset of acute appendicitis symptoms. 2. Patients undergoing interval appendectomy. 3. Patients with malignancy or other inflammatory conditions likely to affect CRP, bilirubin, and MPV 4. Pregnant women. 5. Patients on anticoagulant therapy.

After getting clearance from the ethical committee and informed written consent in the native language of the patient, details of the patients who are diagnosed with acute appendicitis and operated, on with histopathological diagnosis of acute appendicitis or recurrent appendicitis were entered in the questionnaire. Blood samples were obtained from the patients to measure complete hemogram, liver function test, and C-reactive protein before surgery. After surgery, the histopathological report of the patient was obtained from the pathology department to look for evidence of acute appendicitis or recurrent appendicitis.

Statistical analysis was done with SPSS 21 software and data analysis was done with student T test and Mann Whitney test. P value less than 0.05 was significant.

RESULTS

A total of 60 patients with a clinical diagnosis of acute appendicitis were included in study. Data were tabulated on a Microsoft excel sheet and analyzed as below.

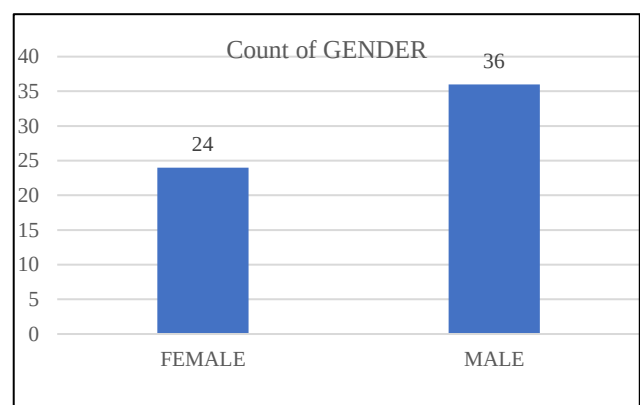


Figure 1: Gender distribution.

Of the 60 patients enlisted for the study, 36 (60%) were males while the remaining 24 (40%) were females.

Table 1: Age distribution.

Variables	Mean	SD
Male	29.78	11.160
Female	27.20	11.544
Total	28.54	11.340

The overall mean age of all 60 patients was 28.54±11.34 years. The average age in females and males was 27.20±11.54 years and 29.78±11.16 years.

Table 2: Mean and SD of CRP in acute appendicitis and recurrent appendicitis.

CRP	N	Mean	SD	P value
AA	42	13.231	4.003	0.017
RA	18	8.647	3.956	
Total	60	11.646	4.390	

When the C reactive protein levels were higher than 6 mg/dl, the occurrence of acute appendicitis was significantly higher than in the patients with levels less than 6 mg /dl, p<0.017.

Table 3: Mean and SD of total bilirubin in acute appendicitis and recurrent appendicitis.

Total bilirubin	N	Mean	SD	P value
AA	42	1.045	0.292	<0.000
RA	18	0.663	0.201	
Total	60	0.912	0.323	

When the total bilirubin levels were ≥1 mg/dl, the occurrence of acute appendicitis was significantly higher than in the patients with levels less than <1 mg /dl. The p<0.001.

Table 4: Mean and SD of MPV in acute appendicitis and recurrent appendicitis.

MPV	N	Mean	SD	P value
AA	42	8.140	2.432	0.742
RA	18	7.905	2.211	
Total	60	8.069	2.353	

The occurrence of acute appendicitis did not have any significant correlation with the MPV levels mg/dl in this study (p=0.742).

The 14 patients having modified Alvarado scores between 5-6 and having appendicitis on HPE reports having raised CRP values in all 14 patients and raised serum bilirubin levels in 2 patients.

Then this concludes that the CRP and serum bilirubin

levels can be used as markers for diagnosis of acute appendicitis along with the modified Alvarado score between 5-6 suggestive of appendicitis possibility.

Table 5: MAS.

MAS (Modified Alvarado score)	CRP	Total bilirubin
6	12	0.9
6	15	1.3
5	9	0.6
5	7	0.9
5	12	1.2
5	8	0.6
5	9	0.8
6	11	1
6	14	0.5
6	11	0.5
5	12	0.4
5	15	0.8
5	12	0.6
5	15	0.6

DISCUSSION

Acute appendicitis is the most common acute abdominal condition with 8% of the population in western countries experiencing it in their lifetime.⁶ Appendectomy is the dictum of olden days “to do when suspected than to delay”. The highest incidence is seen in the twenties and thirties. Appendicitis occurs in equal incidence in both sexes with a male-to-female ratio of 1.4:1. Life table suggests a risk of 12% for men as well as 25% for the women.⁷

The major factor responsible for acute appendicitis is obstruction of the lumen. Fecolith is found in most cases.⁸ Other less common causes are also identified. A vast variety of aerobic and anaerobic organisms is involved. However principal organisms are *Escherichia coli* and *Bacteroids fragilis*.

Through ages diagnosis of appendicitis is essentially clinical. Recent advantages in imaging have made diagnosis comparatively easy. In most clinical settings, due to the patient's presentation during emergencies when imaging facilities are not available.

Hence it is mandatory to operate on a patient based on clinical suspicion as the rule of the day. It is globally estimated that 15-30% of cases are negative appendectomies.^{9,10}

There arises a need for necessary routinely available laboratory markers to confirm the diagnosis.

Recently interest has grown in other inflammatory markers which could help diagnose appendicitis and C-reactive protein is one of them.

Serum bilirubin level elevation will help in the accuracy of clinical diagnosis of acute appendicitis and more importantly help in foreseeing and preventing impending complications of acute appendicitis.

This study was taken up with this thought-is it possible to add serum bilirubin, CRP, and MPV as a new laboratory marker to aid in the diagnosis of acute appendicitis and if so, does it have the credibility to help us foresee an impending complication of the acute appendicitis?

The present study was undertaken to study the relationship between hyperbilirubinemia, CRP, and MPV to evaluate its credibility as a diagnostic marker for acute appendicitis.

The study was conducted in the department of general surgery, heritage institute of medical sciences over a period of 2 years (November 2020-November 2022) on 60 patients who were all admitted with the clinical diagnosis of acute appendicitis, investigated, and had undergone appendicectomy and conformed with histopathological examination.

Kim et al in their study on the evaluation of relationships between blood inflammatory markers and CT findings concluded that total white cell count better detects early appendiceal inflammation and an elevated CRP level better detects perforated appendicitis.¹¹

The study by Hyoung-Min et al by multivariate analysis demonstrated that C-reactive protein was an independent predictor for complicated appendicitis (odds ratio, 1.371; 95% confidence interval, 1.155 to 1.628; $p < 0.001$) The cut-off value of C-reactive protein was set at 7.05 mg/dL by using receiver operating characteristic curve (0.805; sensitivity, 57.6%; specificity, 98.3%).¹²

In conclusion, in patients who have already been diagnosed as having appendicitis and for whom surgery has already been scheduled, if the value of C-reactive protein is higher than 7.05 mg/dL, the surgeon should anticipate complicated appendicitis, decide on an appropriate operation time, select antibiotics, and explain the prognosis to the patient.¹²

The mean value of CRP in acute appendicitis was 13.06 mg/dl which was similar to the results of the study of Jangjoo et al and Han Ping et al.¹³

Fatih et al on patients suspected to have acute appendicitis, it was noted that incorporating CRP increased the diagnostic value of the Alvarado scoring system.¹⁴

Kumar et al show CRP and hyperbilirubinemia can be used to predict appendicular perforation preoperatively and that their roles are comparable and there is no advantage between one over the other.¹⁵

Hyperbilirubinemia is recently postulated as laboratory marker for diagnosing acute appendicitis and determining its severity. Studies have shown that bacterial infection disrupts the production and excretion of bile. Normally in portal circulation bacteria are carried by portal blood to the liver.

It is eliminated by the detoxification or immunological action of reticuloendothelial cells of the liver. In patients with abdominal infections bacterial load in portal blood increases beyond the capacity of Kuffer cell function. Additionally, it may cause damage to hepatocytes which is reflected by the rise in serum bilirubin.¹⁶

The most common organism found in appendicitis is *E. coli*. It is a lipopolysaccharide that can mediate the release of pro-inflammatory cytokines (IL-6, TNF). These cytokines in turn cause canalicular damage resulting in a reduction of bilirubin excretion from the hepatocyte.

Many studies also highlighted that decreased output of bilirubin is not due to defective conjugation but due to defective excretion.

In the current study, hyperbilirubinemia (>1 mg/dl) the occurrence of acute appendicitis was significantly higher than in the patients with levels less than < 1 mg /dl. The $p < 0.00$.

The mean total serum bilirubin in the acute appendicitis patients was 1.045 ± 0.29 mg/dl which was above the normal range (>1.0 mg/dl) and considered for the study, hence indicating the presence of the hyper-bilirubinemia.

MPV is a simple and accurate marker of the functional status of platelets. Higher MPV values usually reflect the augmented production of young platelets and an increased number of large hyper-aggregable platelets. Thus, MPV has been considered a suitable indicator of platelet activation.^{17,18}

As described previously, larger platelets are more reactive. Platelet size is determined at the level of the progenitor cell (i.e., the megakaryocyte), and studies have reported that cytokines, such as interleukin-3 or interleukin-6, influence megakaryocyte ploidy and can lead to the production of more reactive, larger platelets.^{19,20} Thus, platelet volume has been proposed as an indirect marker of increased platelet reactivity.

Additionally, activated platelets release antibacterial peptides; however, some evidence indicates that certain pathogens may have developed a means to exploit activated platelets by binding to their surfaces to establish or propagate infection.²¹

In addition, previous studies have reported an association between changes in the levels of MPV and various non-infectious inflammatory processes, which may suggest

that MPV changes reflect disease activity in inflammation.^{22,23}

Albayrak et al a 226-patient study found a significantly lower MPV level in patients with acute appendicitis compared to the control group.²⁴

They suggested that MPV level may guide the management of patients suspected to have acute appendicitis. They found a cut-off level of below 7.6 fL for MPV. We found a cut-off level of above 7.87 fL in patients with acute appendicitis.

In the present study, MPV was found insignificant in the diagnosis of acute appendicitis.

The 14 patients having modified Alvarado scores between 5-6 and having appendicitis on HPE reports having raised CRP values in all 14 patients and raised serum bilirubin levels in 2 patients.

Then this concludes that the CRP and serum bilirubin levels can be used as markers for diagnosis of acute appendicitis along with the modified Alvarado score between 5-6 suggestive of appendicitis possibility.

Limitations

The study was conducted on a limited patient population of 60. The duration of surgery, complications and post-operative hospital stay were not compared. It excludes below 16 years of age, after 72 hours of onset of symptoms, pregnancy, malignant diseases and inflammatory condition or disease.

CONCLUSION

Serum bilirubin level and CRP estimation, which is a simple, cheap, and easily available laboratory test, can be added to the routine investigations in the diagnosis of severity of acute appendicitis and will help in increasing the accuracy of diagnosing appendicitis and help in decreasing negative appendectomy rates, especially in low modified Alvarado score. MPV was insignificant found in this study. Hyperbilirubinemia and CRP were significantly found in this study to diagnose acute appendicitis. Further studies are needed to develop a scoring system to incorporate bilirubin levels along with CRP in the assessment of the severity of appendicitis, which would be useful in resource-limited hospital settings.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Cusheiri A, Grace PA, Darzi A. Disorders of the small intestine and vermiform appendix. Clinical Surgery. 2nd ed. UK: Blackwell Publishing Ltd. 2010;405.
2. Hamilton Bailey's "Emergency Surgeries", 12th Ed. 1995;438-51.
3. Ramula M, Lakshmipathy N, Karthik A, Krishnamurthy A. A comprehensive study on the diagnostic value of quantitative C-reactive protein measurement of acute appendicitis. J Evol Med Dent Sci. 2016;5(69):4995-9.
4. Whiting JF, Green RM, Rosenbluth AB, Gollan JL. Tumor necrosis factor-alpha decreases hepatocyte bile salt uptake and mediates endotoxin-induced cholestasis. Hepatology. 1995;22:1273-8.
5. Kim JY, Dobson BH, Ng CLH, Thong DW, Arthur T, Parker D. Can normal inflammatory markers rule out acute appendicitis? the reliability of biochemical investigations in diagnosis. ANZ J. Surg. 2020;90:1970-74.
6. Slotboom T, Hamminga JT, Hofker HS, Heineman E, and Haveman JW: Apple Study Group A and Laparoscopic Evaluation. The intraoperative motive for performing a laparoscopic appendectomy on a postoperative histologically proven normal appendix. Scand J Surg. 2014;103:245-48.
7. Adams HL and Jaunoo SS: Hyperbilirubinaemia in appendicitis: The diagnostic value for prediction of appendicitis and appendiceal perforation. Eur J Trauma Emerg Surg. 2016;42:249-52.
8. Pieper R, Kager L, Tidefeldt U. obstruction of the appendix vermiformis causing acute appendicitis: an experimental study in rabbits. Acta Chir Scand. 1982;148:63-72.
9. Jones PF. Suspected acute appendicitis: trends in management over 30 years. British J Surg. 2001;88:1570-7.
10. Lee SL, Walsh AJ, Ho HS. Computed tomography and ultrasonography do not improve and may delay the diagnosis and treatment of acute appendicitis. Arch Surg. 2001;136:556-61.
11. Kim HC, Yang DM, Lee CM, Jin W, Nam DH, Song JY et al. Acute appendicitis: relationships between CT-determined severities and serum white blood cell counts and C-reactive protein levels. Br J Radiol. 2011;84(1008):1115-120.
12. Hyoung-Min M, Beom-Seok P, Duk-Jin M. Diagnostic Value of C-reactive Protein in Complicated Appendicitis. J Korean Soc Coloproctol. 2011;27(3):122-6.
13. Han-Ping W, Ching-Yuang L, Chin-Fu C, Yu-Jun C, Chin-Yi H. Predictive value of C-reactive protein at different cutoff levels in acute appendicitis. Am J Emergency Med. 2016;23:449-53.
14. Dal F, Cicek Y, Pekmezci S, Kocazeybek B, Tokman HB, Konukoglu D et al. Role of Alvarado score and biological indicators of C-reactive protein, procalcitonin, and neopterin in the diagnosis of acute

- appendicitis. *Ulusal travma ve acil cerrahi dergisi. Turk J Trauma Emergency Surg.* 2019;25(3):229-37.
15. Anil KB, Kalyan K, Rehman M. Perforation in acute appendicitis: Evaluation of hyperbilirubinemia and elevated C reactive protein as a predictive factor. *IAIM.* 2017;4:18-23.
 16. Atahan K, Üreyen O, Aslan E. Preoperative diagnostic role of hyperbilirubinemia as a marker of appendix perforation. *J Int Med Res.* 2011;39:609-18.
 17. Park Y, Schoene N, Harris W. Mean platelet volume as an indicator of platelet activation: methodological issues. *Platelets.* 2002;13(5-6):301-6.
 18. Ozdemir O, Soylu M, Alyan O, Geyik B, Demir AD, Aras D et al. Association between mean platelet volume and autonomic nervous system functions: Increased mean platelet volume reflects sympathetic overactivity. *Exp Clin Cardiol.* 2004;9(4):243-7.
 19. Uyanik B, Kavalci C, Arslan ED, Yilmaz F, Aslan O, Dede S et al. Role of Mean Platelet Volume in Diagnosis of Childhood Acute Appendicitis. *Emergency Med Int.* 2012;2012:4.
 20. Sartelli M, Viale P, Catena F. 2013 WSES guidelines for the management of intra-abdominal infections. *World J Emerg Surg.* 2013;8(1):3.
 21. Yeaman Michael R. Bacterial-platelet interactions: virulence meets host defense. *Future Microbiol.* 2010;5(3):471-506.
 22. Kapsoritakis AN, Koukourakis MI, Sfiridaki A, Potamianos SP, Kosmadaki MG, Koutroubakis IE et al. Mean platelet volume: a useful marker of inflammatory bowel disease activity. *Am J Gastroenterol.* 2001;96(3):776-81.
 23. Kisacik B, Tufan A, Kalyoncu U, Karadag O, Akdogan A, Ozturk MA et al. Mean platelet volume (MPV) as an inflammatory marker in ankylosing spondylitis and rheumatoid arthritis. *Joint Bone Spine.* 2008;75(3):291-4.
 24. Albayrak Y, Albayrak A, Albayrak F, Yildirim R, Aylu B, Uyanik A et al. Mean Platelet Volume: A New Predictor in Confirming Acute Appendicitis Diagnosis. *Clin Appl Thrombosis/Hemostasis.* 2011;17(4):362-66.

Cite this article as: Mahendra TS, Agrawal S. Role of C reactive protein, hyperbilirubinemia and mean platelet volume in diagnosis of acute appendicitis and its correlation post operatively with histopathological examination. *Int Surg J* 2023;10:1182-7.