



Platelet Indices in the Diagnosis of Acute Appendicitis

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Abstract

Background: The aim of this study was to evaluate the diagnostic value of platelet indices (mean platelet volume and platelet distribution width) and its predictive value in determining the complication/severity of acute appendicitis.

Method: This study comprised of 126 adult patients of Acute Appendicitis who were operated in the department of Surgery, Zoram Medical College, Falkawn during the period of two years starting from March 2017 to April 2018. Patients below 12 years, pregnant female, patients on steroid/chemotherapy, immuno-compromised patients and those who are not willing to participate were excluded.

Results: The Mean Platelet Volume (MPV) of less than 7.6 was found in 73 (57.9%). The mean MPV was 7.98 ± 1.29 . Platelet Distribution Width (PDW) was more than 18 patients (23.7%). Out of which 16 and 14 were females and males respectively. The mean PDW was 16.99 ± 2.30 . Total Leucocyte Count (TLC) was raised (taking 1,100 as cut-off value) in 82 patients (65.1%). 11 patients were associated with perforated appendix and 10 patients had intraoperative finding of periappendiceal collection. Gangrenous appendix was found in 16 (12.7%) patients.

Conclusion: MPV did not have higher sensitivity compared with TLC in the diagnosis of acute appendicitis but PDW have higher sensitivity than TLC and is found higher in complicated appendicitis. Therefore, PDW may be used in the diagnosis of acute appendicitis and has a significant role in predicting complicated appendicitis.

Keywords: Acute appendicitis; Mean platelet volume; Platelet distribution width; Total leucocyte count; Perforated appendix

Introduction

Acute Appendicitis (AA) is the most common general surgical emergency. The diagnosis of acute appendicitis can be elusive, and high index of suspicion is important in preventing serious complication from this disease. Approximately 8% of those in Western countries have appendicitis at sometime during their life, with a peak incidence between 10 to 30 years of age. Whereas the diagnosis of acute appendicitis is usually established clinically, the symptoms and findings may not always be typical, in which case the establishment of diagnosis becomes difficult [1].

The vermiform appendix is present only in humans, certain anthropoid apes. It is a blind muscular tube with mucosal, sub-mucosal, muscular and serosal layers. The position of the base of the appendix is constant, being found at the confluence of the three taenia coli of the caecum, which fuse to form the outer longitudinal muscle coat of the appendix. The average length of the appendix is between 7.5 cm and 10 cm. The various positions of the appendix are Retrocaecal (74%), Pelvic (21%), Paracaecal (2%), Subcaecal (1.5%), Preileal (1%), Postileal (0.5%) [2].

Rapid and accurate diagnosis is important because extension of the period between the initiation of the symptoms and start of the surgical procedure increases the risk for appendiceal perforation, thereby potentially resulting in sepsis and even death. In addition, the ratio of patients undergoing appendectomy with a normal histopathologic investigation result (negative appendectomy) ranges between 5% and 42%. The morbidity of these patients who are operated on despite the absence of acute appendicitis is thus increased. The rate of clinical diagnosis of acute appendicitis is approximately 85% [3]. Although current advanced imaging methods such as Ultrasonography (USG), computed tomography and magnetic resonance imaging are promising, they are not adequate. Therefore, novel methods that differentiate acute appendicitis from nonspecific abdominal pain and reduce the rate of negative appendectomy are needed. Such methods should be inexpensive and convenient, with results obtained in a short time.

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The first reported case of appendicitis appeared in 1554, when Jean Fernel noted at autopsy the luminal obstruction, necrosis, and perforation of the appendix and caecum. In 1886, Reginald Fitz demonstrated that the appendix was the primary site and source of inflammation in perityphlitis and endorsed early surgical intervention and appendectomy as imperative for cure, and coined the term appendicitis. In 1889, McBurney presented his successful experience involving early removal of the appendix, and helped to improve the method of early clinical diagnosis with his description regarding McBurney's point. Both Fitz and McBurney's work were instrumental in leading to the advocacy of early operative intervention, which by 1901 proved to reduce the mortality of acute appendicitis from 50% to 15%. Subsequent advances in anesthesia, antibiotics, surgical techniques, and diagnostic modalities have further reduced the incidence of total morbidity and mortality associated with acute appendicitis to 10% to 20% and 0.18% to 0.8%, respectively [4].

To supplement the clinical diagnosis and to reduce the frequency of unnecessary appendectomy, the importance of laboratory investigations like White Blood Cell (WBC) counts and C-Reactive Protein (CRP) values etc has been stressed. The use of Ultrasonography (USG) as a diagnostic tool for appendicitis has been widely known and studied various scores combining clinical features and laboratory investigations have also been developed and are good enough to reach the diagnosis. These are the Alvarado score and the Modified Alvarado score. The sensitivity, specificity, positive predictive value, negative predictive value and accuracy rate of Ultrasonography was 71.2%, 83.3%, 97.4%, 25% and 72.4%, respectively [5].

The Alvarado score is a clinical scoring system used to stratify the risk of appendicitis in patients presenting with abdominal pain. Alvarado's original work was published in 1988 and is based on his retrospective data analysis of 305 patients presenting with abdominal pain suggestive of acute appendicitis. This study found eight predictive factors of diagnostic value in acute appendicitis and assigned each factor a value of 1 or 2 based on their diagnostic weight. A score of 1 was given for each of the following: elevated temperature $>37.3^{\circ}\text{C}$, rebound tenderness, migration of pain to Right Lower Quadrant (RLQ), anorexia, nausea or vomiting, and leukocyte left shift. A score of 2 was given for RLQ tenderness and leukocytosis $>10,000$. The likelihood of appendicitis and specific management recommendations are given based on the total score. A score of 5 or 6 is "compatible" with the diagnosis of acute appendicitis and recommends the clinician observe or serially examine the patient. A score of 7 or 8 is "probable" appendicitis and a score of 9 or 10 is "very probable" appendicitis and recommends surgical intervention [6].

White blood cell counts were found to be high ($>10,500/\text{mm}^3$) in 80% while it was 83% for acute appendicitis group and 61% for Negative Appendectomy (NA) group ($p>0.05$). There were 66 (34%) patients who had no USG findings for acute appendicitis. Of these, 46 (70%) patients were observed to have histologically proved acute appendicitis. There were 130 patients who had positive USG findings for acute appendicitis and 11% of these had histologically normal appendix. Negative Appendectomy Rate (NAR) was 17.3%; this rate was 11.5% for male and 27% for female patients ($p=0.003$). Negative Appendectomy Rate (NAR) decreased to 7.6% when white blood cell count was high and USG findings were confirming appendicitis, whereas NAR was 46% in the patients who had normal white blood cell counts and normal USG findings [7].

Recent studies have investigated the diagnostic accuracy of

inflammatory markers. Mean Platelet Volume (MPV) and Platelet Distribution Width (PDW) are presented in the complete blood cell count, which is routinely used in emergency departments. They are the indicators of platelet activation. The size of the platelet is correlated with the activity and the function of the platelet; larger platelets are more active than small ones. Thus, MPV may be used as a biomarker in myocardial infarction, diabetes mellitus, inflammatory disorders, sepsis-like conditions, myeloproliferative diseases, massive hemorrhage, leukemia, vasculitis and post-splenectomy conditions. Platelet distribution width is an indicator of variation in platelet size, which can be a sign of active platelet release. Studies have demonstrated that in addition to MPV, PDW is also altered compared to healthy subjects in several conditions [3].

Mean platelet volume is a measure of platelet size generated by full blood count analyzer as a part of routine Complete Blood Count (CBC). Mean platelet volume is decreased in acute inflammation of Gastro-intestinal tract. The reason given is consumption and sequestration of platelets in vascular segment of inflamed bowel. The introduction of mean platelet volume in the battery of investigation for the diagnosis of acute appendicitis can aid in increasing the accuracy [8].

Dinc B et al. [3] found that the highest diagnostic accuracy detected was for platelet distribution width. The sensitivity, specificity and diagnostic accuracy were 73.1%, 94.0% and 78% for white blood cell count, 70.0%, 96.0% and 76.0% for neutrophil percentage, 29.5%, 49.0% and 34.0% for mean platelet volume and 97.1%, 93.0% and 96.0% for platelet distribution width respectively. Platelet distribution width analysis can be used for diagnosis of acute appendicitis without requiring additional tests, thus reducing the cost and loss of time. Diagnostically, the sensitivity, specificity and diagnostic accuracy were 73.1%, 94.0% and 78% for white blood cell count, 70.0%, 96.0% and 76.0% for neutrophil percentage, 29.5%, 49.0% and 34.0% for mean platelet volume and 97.1%, 93.0% and 96.0% for platelet distribution width respectively. There are very few studies investigating the diagnostic accuracy of platelet function parameters in cases of acute appendicitis. In view of the above context, the present study was undertaken to assess platelet indices in the diagnosis of acute appendicitis and complication.

Materials and Methods

The study was conducted in the department of General Surgery, State Referral Hospital of Zoram Medical College, Falkawn, Mizoram, India, during the period of March 2017 to April 2019. Before taking up the study, approval for carrying out the research work was obtained from the Institute Ethical Committee. Confidentiality and privacy was maintained. It is an observational (cross sectional) study of 126 patients with acute appendicitis who underwent Appendectomy. Patients of more than 12 years attending hospital with a clinical diagnosis of acute appendicitis and undergoing appendectomy, those who are willing to participate were included. Exclusion criteria were pregnant female, patients on steroid, immuno-compromised patients, patients on chemotherapy for malignancy those who are not willing to participate. The study was conducted under some variables such as age, sex, MPV and PDW, duration of symptom and diagnosis (clinical/operative). All patients admitted with clinical diagnosis of "Acute Appendicitis" or "Appendicular Perforation" under General Surgery was taken as Subjects for this study. Informed Consent was collected using the questionnaire/proforma. The primary data for this study was the blood investigations of the patients *viz.* Routine blood

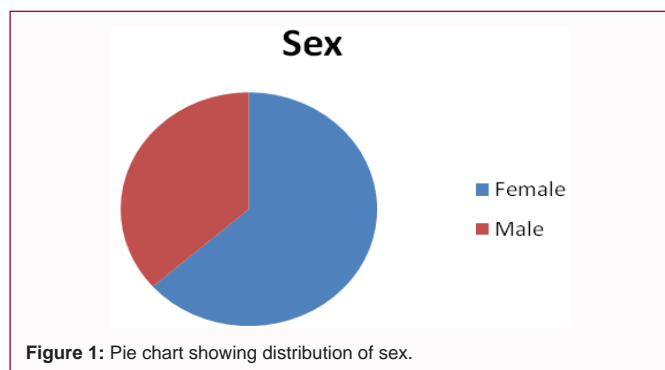


Figure 1: Pie chart showing distribution of sex.

Table 1: Age distribution of patients studied.

Age in years	Gender		Total
	Male	Female	
20-Nov	6 (13%)	18 (22.5%)	24 (19%)
21-30	19 (41.3%)	31 (38.8%)	50 (39.7%)
31-40	13 (28.3%)	13 (16.3%)	26 (20.6%)
41-50	6 (13%)	5 (6.3%)	11 (8.7%)
51-60	1 (2.2%)	9 (11.3%)	10 (7.9%)
>60	1 (2.2%)	4 (5%)	5 (4%)
Total	46 (100%)	80 (100%)	126 (100%)

Table 2: Periappendiceal collection distribution of patients studied.

AC	Gender		Total
	Male	Female	
Non Collection	41 (89.1%)	75 (93.8%)	116 (92.1%)
Collection	5 (10.9%)	5 (6.3%)	10 (7.9%)
Total	46 (100%)	80 (100%)	126 (100%)

Table 3: Perforated appendix distribution of patients studied.

AP	Gender		Total
	Male	Female	
Non Perforated	41 (89.1%)	74 (92.5%)	115 (91.3%)
Perforated	5 (10.9%)	6 (7.5%)	11 (8.7%)
Total	46 (100%)	80 (100%)	126 (100%)

investigations (i.e. complete blood count, platelet count, reticulocyte count etc.), Platelet indices; MPV and PDW, Urine examination (routine & microscopy). Data collected included age, sex, duration of symptoms, clinical operative diagnosis and platelet indices. Clinical diagnosis was confirmed by histopathology. Clinical and investigative data was compiled and analyzed, and observed. Routine MPV and PDW results were compared with laboratory reference values. All the data was entered in a proforma and data analysis was performed using SPSS software 21 version (IBM Corp., Armonk, NY, United States). A statistical analysis was performed with Student's t-test and the chi square test. A P value of 0.05 or less was considered significant. After obtaining consent, patients were operated, and the appendectomy specimen was sent for histopathological examination. The histopathology report was considered as the final diagnosis. All blood samples were obtained from the venous system and stored in tubes containing EDTA and assayed automatically using internationally certified devices ABX Pentra 60, Manufactured by Horiba medical, France on August 2005. The reference values are 7.6-

11.0 fL for MPV and 10% to 18% for PDW. All results were approved by an independent pathologist expert who was blind to the patient's histories.

Results and Observation

Out of 126 patients, 46 (36.5%) were males and 80 (63.5%) were females. The mean age of patient was 31.67 ± 12.66 , ranging from 15-64 years. The highest number of patients was found in 21 to 30 age groups (39.7) (Table 1) (Figure 1).

Out of 126 cases studied, 11 patients of all acute appendicitis were associated with perforated Appendix (AP) and 10 patients had intra-operative finding of periappendiceal Collection (AC). Gangrenous Appendix (AG) was found in 16 (12.7) patients. All the patients diagnosed with acute appendicitis were proven with positive Histopathological Examination (HPE) (Tables 2-5).

Out of 126 patients, TLC was raised (taking 1,100 as cut-off value) in 82 patients i.e. 65.1%. The mean TLC was 1335.56 ± 625.18 , out of which 33 and 49 were males and females respectively. MPV of less than 7.6 was found in 73 i.e. 57.9%. The mean MPV was 7.98 ± 1.29 . PDW was more than 18 in 30 patients i.e. 23.7%, out of which 16 and 14 were females and males respectively. The mean PDW was 16.99 ± 2.30 (Tables 6-9).

Statistical methods

Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean \pm SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5% level of significance. The following assumptions on data are made.

Assumptions

1. Dependent variables should be normally distributed, 2. Samples drawn from the population should be random, 3. Cases of the samples should be independent. Student t test (two tailed, independent) has

Table 4: Gangrenous appendix distribution of patients studied.

AG	Gender		Total
	Male	Female	
Non Gangrene	38 (82.6%)	72 (90%)	110 (87.3%)
Gangrene	8 (17.4%)	8 (10%)	16 (12.7%)
Total	46 (100%)	80 (100%)	126 (100%)

Table 5: HPE distribution of patients studied.

HPE	Gender		Total
	Male	Female	
Negative	0 (0%)	0 (0%)	0 (0%)
Positive	46 (100%)	80 (100%)	126 (100%)
Total	46 (100%)	80 (100%)	126 (100%)

Table 6: Total leucocyte count (TLC) distribution of patients studied.

Total leucocyte count	Gender		Total
	Male	Female	
<400	0 (0%)	0 (0%)	0 (0%)
400-1100	13 (28.3%)	31 (38.8%)	44 (34.9%)
>1100	33 (71.7%)	49 (61.3%)	82 (65.1%)
Total	46 (100%)	80 (100%)	126 (100%)

Table 7: Total Platelet Count (TLC) distribution of patients studied.

Total Platelet Count	Gender		Total
	Male	Female	
<1.5	1 (2.2%)	1 (1.3%)	2 (1.6%)
1.5-4	45 (97.8%)	79 (98.8%)	124 (98.4%)
>4	0 (0%)	0 (0%)	0 (0%)
Total	46 (100%)	80 (100%)	126 (100%)

Table 8: Mean Platelet Volume (MPV) distribution of patients studied.

Mean Platelet Volume	Gender		Total
	Male	Female	
<7.6	28 (60.9%)	45 (56.3%)	73 (57.9%)
7.6-11	18 (39.1%)	35 (43.8%)	53 (42.1%)
>11	0 (0%)	0 (0%)	0 (0%)
Total	46 (100%)	80 (100%)	126 (100%)

Table 9: Platelet Distribution Width (PDW) distribution of patients studied.

Platelet Distribution Width	Gender		Total
	Male	Female	
<10	0 (0%)	0 (0%)	0 (0%)
18-Oct	32 (69.6%)	64 (80%)	96 (76.2%)
>18	14 (30.4%)	16 (20%)	30 (23.7%)
Total	46 (100%)	80 (100%)	126 (100%)

been used to find the significance of study parameters on continuous scale between two groups (Inter group analysis) on metric parameters. Leven I s test for homogeneity of variance has been performed to assess the homogeneity of variance. Chi-square/Fisher exact test has been used to find the significance of study parameters on categorical scale between two or more groups, non-parametric setting for Qualitative data analysis. Fisher exact test used when cell samples are very small. Logistic regression analysis was employed to find the correlation of positivity with clinical variables (Adj OR=1, no relationship, Adj OR>1, positive association and Adj OR<1: Negative association). ROC curve analysis is performed to find the predictability of study variables for predicting the outcome. In comparison with TLC (taking 1,100 as standard cut-off value), sensitivity and specificity of MPV is 64.38% and 35.9% respectively. And also sensitivity and specificity for PDW in comparison with TLC is 86.2% and 46.15% respectively.

Discussion

Even though the Acute Appendicitis (AA) presents with the classical symptomatology, it is still considered among one of the difficult entities to diagnose. There are many diagnostic entities which are being studied extensively in relation to AA and others. One of such parameters is Mean Platelet Volume (MVP) and Platelet Distribution Width (PDW). MVP has been studied as an inflammatory marker in several diseases. MPV represents an index of

platelet function. An increase in young platelets and an aggregation of large platelets could lead to higher MPV values. Platelets size and activity are influenced by cytokines, such as IL-3 or IL-6. In many chronic diseases, the MPV increases, while in many acute diseases the MPV decreases. Specifically, the MPV decreases in patients with ulcerative colitis, rheumatoid arthritis, and ankylosing spondylitis, land the MPV increases in patients with ankylosing spondylitis, familial Mediterranean fever, Behcet’s disease and Psoriasis [9].

Makay B et al. [10] found no significantly different MPV levels in control and patient groups but a decreased MPV level was detected at the time of attack, in patent group in a pediatric patient cohort of familial mediterranean fever. Albayrak Y et al. [11] detected a significantly lower MPV level in patients with AA, compared to the control group. Another study by Bilici S et al. [12] found similar result in children.

This study investigated diagnostic value of MPV and PDW in acute appendicitis, taking TLC as a standard value, sensitivity and specificity for MPV is 64.38% and 35.9% respectively, and taking less than 7.6 as a cut-off value for MPV. And also sensitivity and specificity for PDW is 86.2% and 46.15% respectively, and taking more than 18 as a cut-off value for PDW.

In study conducted by Albayrak Y et al. [11] and Aydogan A et al. [13] MPV was significantly lower in the AA group, and with a sensitivity and specificity of 73% to 84% and 54% to 84% respectively in children. The values of sensitivity and specificity of MPV in our study are 64.3% and 35.9% respectively and lower as compared to the literature. Our study detects a higher sensitivity and lower specificity of MPV, compared to the finding of Albayrak Y et al. [11] study. Albayrak Y et al. [11] and Aydogan A et al. [13] in their previous study had shown the increase in PDW in acute appendicitis. In our study, there is also increase in PDW value taking more than 18 as a cut-off value. Sensitivity and specificity of PDW were 86.2% and 46.15% respectively, which was comparable with literatures and previous study.

In the study conducted by Zhe F et al. [14] PDW was significantly raised in acute gangrenous appendicitis. And also Dinc B et al. [3] in their study confirmed that PDW was significantly higher in perforated appendicitis. Also Aydogan A et al. [13] found that MPV and PDW were important markers for the early detection of perforation risk in acute appendicitis.

We also had conducted a study on MPV and PDW in relation with complicated appendicitis like perforation and gangrenous appendix. In our study we found that, the sensitivity and specificity for MPV in perforated appendix is 60.0% and 46.04% respectively which is not very significant. In contrast, the sensitivity and specificity of PDW in perforated appendix is 90.91% and 93.91% respectively with a significant p value of 0.001. ROC curve analysis of MPV and PDW with regard to perforated appendix is shown below Table 10.

Table 10: ROC curve analysis of TLC, TPC, MPV, PDW in perforated appendix.

Variables	ROC results to predict AG (perforated)				Cut-off	AUROC	SE	P value
	Sensitivity	Specificity	LR+	LR-				
Total leucocyte count	87	80	5	0	>1110	0.926	0.024	<0.001**
Total platelet count	81.82	89.57	7.57	0.2	≤ 1.8	0.891	0.056	<0.001**
Mean platelet volume	60	46.04	2.13	0	≤ 7.4	0.762	0.051	<0.001**
Platelet distribution width	90.91	93.91	10.45	0.39	>18	0.906	0.042	<0.001**

Table 11: ROC curve analysis of TLC, TPC, MPV and PDW in gangrenous appendix.

Variables	ROC results to predict GAI (Gangrene)				Cut-off	AUROC	SE	P value
	Sensitivity	Specificity	LR+	LR-				
Total leucocyte count (TLC)	86.09	82.88	5.84	0	>1100	0.943	0.02	<0.001**
Total platelet count (TPC)	80	75.68	3.29	0.26	≤ 2.0	0.814	0.065	<0.001**
Mean platelet volume (MPV)	63.33	54.05	2.03	0.12	≤ 7.4	0.766	0.052	<0.001**
Platelet distribution width (PDW)	88.67	84.7	5.66	0.16	>18.0	0.871	0.062	<0.001**

We also compared and evaluated the relationship between gangrenous appendix with MPV and PDW. The sensitivity and specificity of PDW in gangrenous appendix are 88.67% and 84.67% respectively, which is significant with a p value of 0.001. In contrast, MPV has sensitivity and specificity of only 63.33% and 54.05% respectively. The ROC curve of MPV and PDW with regard to gangrenous appendix is shown below Table 11.

Conclusion

We found that the MPV with sensitivity and specificity of 64.38% and 35.9% respectively did not have higher sensitivity compared with TLC in the diagnosis of acute appendicitis. But interestingly, PDW with a sensitivity and specificity of 86.2% and 46.15% have higher sensitivity than TLC. And also PDW level with sensitivity of 90.91% and specificity of 93.91% is found higher in complicated appendicitis like perforated appendix and gangrenous appendix. So, we concluded that MPV is not significant, while PDW may be used in diagnosis of acute appendicitis and has a significant role in predicting complicated appendicitis.

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