

Can mean platelet volume, Neutrophil-to-Lymphocyte, Lymphocyte-to-Monocyte, Platelet-to-Lymphocyte ratios be favourable predictors for the differential diagnosis of appendicitis?

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Abstract

Objective: To investigate whether some ratios obtained from complete blood count could be favourable predictors in differentiating appendicitis from mesenteric lymphadenitis, appendicitis and familial Mediterranean fever.

Methods: The retrospective cross-sectional study was conducted at AfyonKocatepe University Medical Faculty, Afyonkarahisar, Turkey, from January 1, 2014, to December 31, 2016, and comprised data of patients who presented to the department of paediatric surgery and paediatrics with symptoms of acute abdomen. Mean platelet volume, neutrophil/lymphocyte ratio, lymphocyte/monocyte ratio, and platelet/lymphocyte ratio of the patients calculated at the time of admission were analysed. SPSS 20 was used for data analysis.

Results: Of the 301 patients, there were 139(46.2%) males and 162(53.8%) were females. The overall mean age was 11.5 ± 4.33 years. Of the total, 137(45%) had appendicitis, 65(22%) familial Mediterranean fever, and 99(33%) had mesenteric lymphadenitis. Mean platelet volume was significantly different among the study groups ($p < 0.05$). Neutrophil/lymphocyte ratio and platelet/lymphocyte ratio were statistically significantly higher ($p < 0.05$) while lymphocyte/monocyte ratio was significantly lower ($p < 0.05$) in appendicitis cases compared to the others.

Conclusion: Mean platelet volume, neutrophil/lymphocyte ratio and platelet/lymphocyte ratio were found to be the potent predictors for the differential diagnosis of familial Mediterranean fever and mesenteric lymphadenitis which are mostly confused with appendicitis.

Keywords: Blood cell count, Familial Mediterranean fever, Mesenteric lymphadenitis, Appendicitis. (JPMA 69: 647; 2019)

Introduction

Acute appendicitis is the most commonly encountered cause of acute abdomen and surgical abdomen at paediatric age.¹ Although it occurs less frequently under five years of age, its lifetime risk is 7%.² Appendicitis can be confused with many surgical or non-surgical diseases. For a differential diagnosis, we need a physical examination and a detailed medical history together with imaging methods or blood tests. The search for the most reliable, inexpensive, easily applicable, non-invasive and easily accessible investigation which will direct the patient to the correct treatment without causing loss of time continues. Therefore, studies on using laboratory inflammatory markers as predictive agents in order to clarify the diagnosis of acute abdomen have increased in numbers.³⁻⁵

The current study was planned to investigate whether some inflammatory markers in the blood could be

favourable predictors in differentiating appendicitis from mesenteric lymphadenitis (ML) and familial Mediterranean fever (FMF).

Subjects and Methods

The retrospective cross-sectional study was conducted at Afyon Kocatepe University Medical Faculty, Afyonkarahisar, Turkey, from January 1, 2014, to December 31, 2016, and comprised data of patients who presented to the department of paediatric surgery and paediatrics with symptoms of acute abdomen. After obtaining permission from the institutional ethics committee, data was retrieved from the hospital registry. Record of patients who underwent surgery due to appendicitis or who were followed up due to FMF and ML were identified. Data was divided into three disease-based groups. The appendicitis group had patients whose diagnoses were confirmed histopathologically as appendicitis after appendectomy. The FMF group consisted of patients who had abdominal pain, in whom appendicitis was ruled out, but who were found to have symptoms consistent with FMF genetically and clinically upon further investigation and after treatment. The ML group had patients who had acute abdomen signs, in

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whom appendicitis was ruled out after physical examination and investigations, and in whom mesenteric lymphadenitis was detected with ultrasound (US). When the short axis of the lymph node was above 10mm in US, the patient was included in the study⁶ (Figure-1).

Those excluded were patients with heart failure, peripheral vascular disease, haematological disease, liver disease, anticoagulant and steroid use, acute or chronic another infection site.

The complete blood count (CBC) parameters at admission to the clinic, US reports, pathology reports, genetic and fibrinogen results were recorded. Mean platelet volume (MPV), neutrophil/lymphocyte ratio (NLR), lymphocyte/monocyte ratio (LMR) and platelet/lymphocyte ratio (PLR) values were calculated. CBC data was assessed from the records. Absolute neutrophil, platelet, lymphocyte, and monocyte counts, and MPV values were derived from the CBC measurements. NLR, PLR, and LMR were calculated as follows: NLR=Absolute neutrophil count/absolute lymphocyte count; PLR=Absolute platelet count/absolute lymphocyte count; and LMR=Absolute lymphocyte count/absolute monocyte count. These values were compared among the three groups.

The US findings of the patients were examined. The preoperative US and postoperative pathology reports

were compared. The sensitivity and specificity of US compared to pathology reports were assessed with respect to the differential diagnosis of appendicitis. The efficacies of other parameters in differential diagnosis were compared by taking US and total white blood cell (WBC) count as references.

Mindray BC-6800 (Mindray Building, Shenzhen, China) device was used for the analyses of blood parameters. Appendicitis and ML were explored with an US device (Hi Vision Preir, EZU-MT28-S1, Hitachi, Japan).

Data were analysed using SPSS 20. Data distribution was tested by Shapiro-Wilk test. Upon detecting that the data did not distribute normally, nonparametric Kruskal-Wallis test was used for group comparisons. While determining different groups, Dunn pair wise comparison test was used as post-hoc test. The Receiver operating characteristic (ROC) curve analysis was performed for sensitivity and specificity. Logistic regression analyses were performed. P<0.05 was considered statistically significant.

Results

Of the 301 patients, there were 139(46.2%) males and 162(53.8%) were females. The overall mean age was 11.5±4.33 years. There was a significant difference related to age distribution in the groups (p=0.001). Of the total,

Table-1: The characteristics of patients with appendicitis (n:137), FMF (n:65), and mesenteric lymphadenitis (n:99).

	Appendicitis	FMF	Mesenteric Lymphadenitis	P *	P**
Gender (M/F)	63/74	24/41	52/47	0.116 (Chi Square test)	
Age (years)	12.07± 3.89	11.25±4.47	9.82±4.51	0.001 (Chi Square test)	A-FMF:0.216 A-ML:0.001 ML-FMF:0.044 A-FMF:0.001 A-ML:0.001 ML-FMF:0.925 A-FMF:0.199 A-ML:0.003 ML-FMF:0.198 A-FMF:0.001 A-ML:0.001 ML-FMF:0.050 A-FMF:0.001 A-ML:0.001 ML-FMF:0.149 A-FMF:0.001 A-ML:0.001 ML-FMF:0.178
WBC (×10 ³ /μl)					
Mean±SD	16.16±4.97	11.60±6.23	11.11±4.74	0.001	
Average rank	195.15	113.59	112.33		
MPV (fl)					
Mean±SD	8.12±1.65	8.92±8.93	7.75±0.99	0.011	
Average rank	164.47	147.76	138.04		
NLR					
Mean±SD	12.48±11.09	3.39±4.17	5.05±6.08	0.001	
Average rank	200.71	91.38	118.34		
LMR					
Mean±SD	2.36±2.16	4.86±3.91	4.11±2.74	0.001	
Average rank	109.39	195.46	175.53		
PLR					
Mean±SD	239.85±152.71	147.24±95.32	178.62±134.58	0.001	
Average rank	181.59	110.45	129.09		

*P values of Kruskal-Wallis test

**P values of Dunn pairwise comparisons test

A: Appendicitis; FMF: Familial Mediterranean Fever; ML: Mesenteric Lymphadenitis; WBC: White blood cell count; MPV: Mean platelet volume; NLR: Neutrophil-to-lymphocyte ratio; LMR: Lymphocyte-to-monocyte ratio; PLR: Platelet-to-lymphocyte ratio; SD: Standard deviation; M: Male; F: Female.

Table-2: Comparisons of the sensitivity, specificity, odds ratio, classification accuracy rates of mean platelet volume (MPV), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR) with ultrasound (US) and white blood cell count (WBC).

Parameters (cut-off values)	Sensitivity %	Specificity %	Odds ratio	95% CI	Classification accuracy rate %
US	91.25	60	15.63	2.22-109.95	89.41
WBC ($13.05 \times 10^3/\mu\text{l}$)	76	74	1.20	0.785-0.874	74.2
MPV (7.65 fL)	69	59	1.006	0.952-1.063	56.4
NLR (3.50)	86	60	1.19	0.803-0.885	74
LMR (2.86)	25	34	1.454	1.274-1.660	70.6
PLR (120.000)	85	43	1.004	0.993-0.998	64

CI: Confidence Interval; US: Ultrasonography; WBC: White blood cell count; MPV: Mean platelet volume; NLR: Neutrophil-to-lymphocyte ratio; LMR: Lymphocyte-to-monocyte ratio; PLR: Platelet-to-lymphocyte ratio.

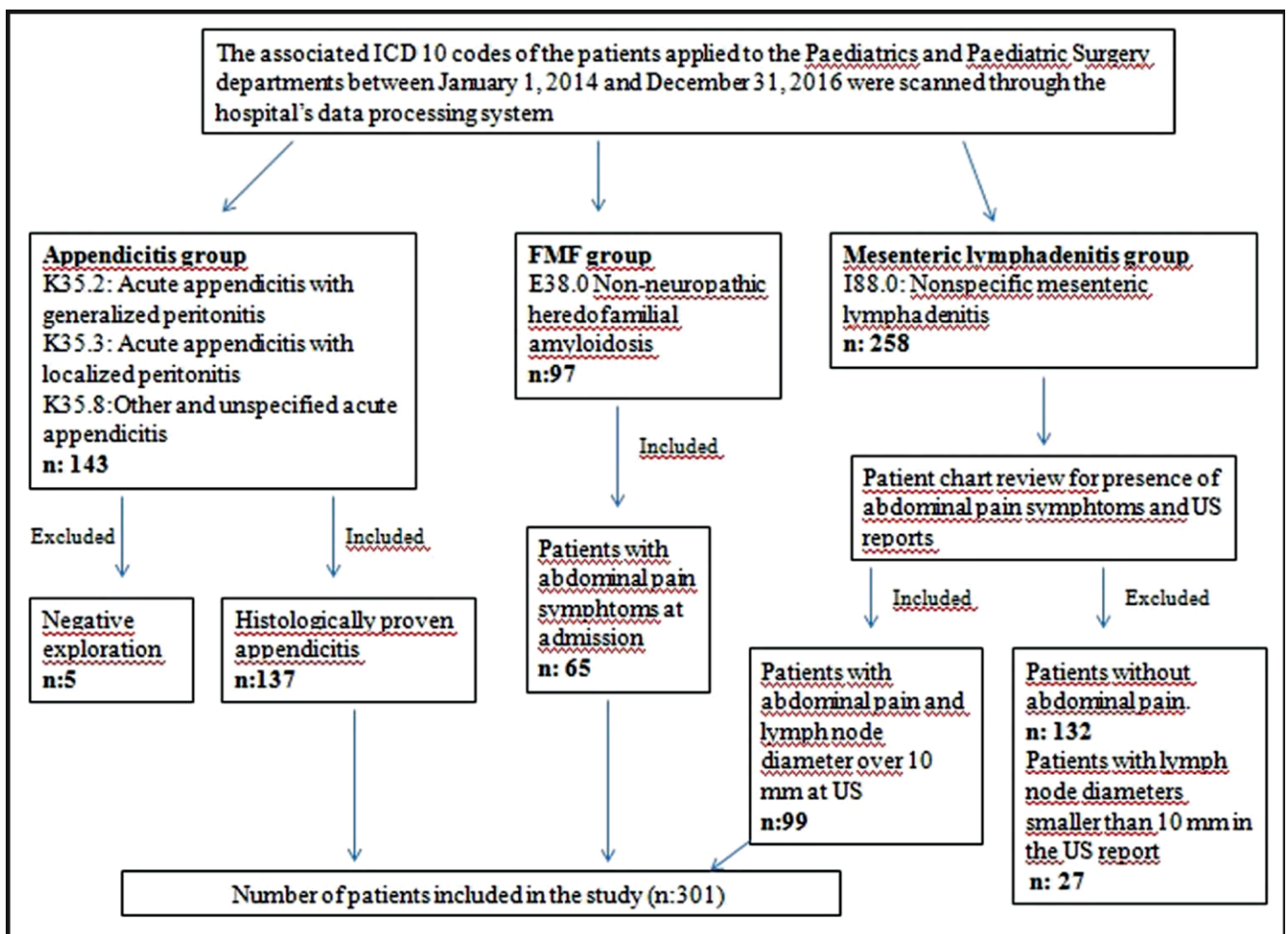


Figure-1: Patient flow chart.

137(45%) had appendicitis, 65(22%) FMF, and 99(33%) had ML. US was found to have a sensitivity of 91.25%, a specificity of 60% and a classification accuracy rate of 89.41%.

WBC, MPV, NLR, LMR, PLR values were noted (Table-1).

Comparing the appendicitis group with ML and FMF groups, the WBC value was significantly higher ($p=0.001$). There was no difference between the FMF and ML groups ($p=0.925$). When the cut-off value was taken as $13.05(\times 10^3/\mu\text{l})$, WBC was found to have the sensitivity and specificity of 76% and 74%. The area lying under the curve

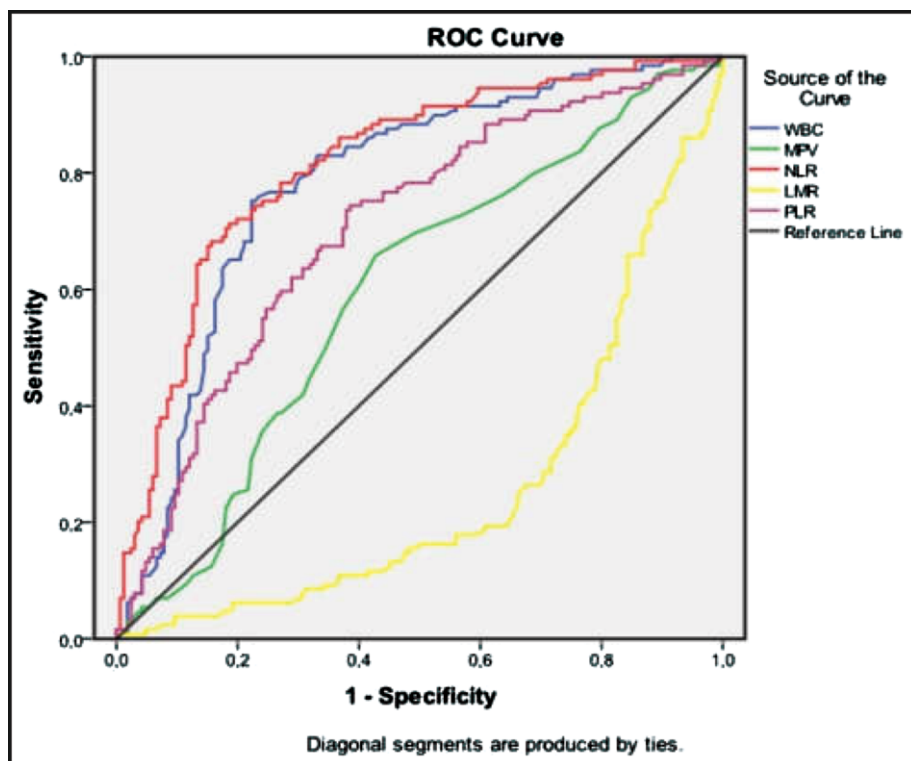


Figure-2: The Receiver Operating Curve (ROC) of mean platelet volume (MPV), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), and white blood cell count (WBC); NLR was even better than WBC, PLR, and MPV can be used for differential diagnosis but LMR is not very significant in differential diagnosis since it had a low value for the area under curve (Area under the curve for the variables: WBC = 0.782; MPV = 0.590; NLR = 0.814; LMR = 0.259; PLR = 0.704).

(AUC) for WBC was 0.782 and its classification accuracy rate was 74.2% (Figure-2).

MPV differed among the study groups ($p=0.011$). MPV value in the appendicitis group was significantly higher compared to the ML group ($p=0.003$). The appendicitis and FMF groups had no significant difference ($p>0.05$). When the cut-off value was set at 7.65fL, the MPV was found to have sensitivity 69% and specificity 59%. The AUC was 0.590 and its classification accuracy rate was 56.4%.

The mean value and average rank of NLR were quite high in the appendicitis group compared to the other groups ($p=0.001$ each). FMF and ML groups did not provide any significant difference ($p=0.05$). When the cut-off value was set at 3.5, NLR had sensitivity 86%, and specificity 60%. The AUC was 0.814 and its classification accuracy rate was 74%.

LMR of the appendicitis group was significantly lower than those in the other groups ($p=0.001$ each), but no significant difference could be found between FMF and ML groups ($p=0.149$). When the cut-off value was set at

2.86, LMR had sensitivity 25%, and specificity 34%. The AUC was 0.259 and its classification accuracy rate was 70.6 %.

Compared to ML and FMF groups, PLR in the appendicitis group was significantly higher ($p=0.001$ each). FMF and ML groups did not show significant difference ($p>0.05$). When the cut-off value was set at 120,000, PLR had sensitivity 85%, and specificity 43%. The AUC was 0.704 and the rate of its classification accuracy was 64%. Sensitivity, specificity, odds ratio (OR), 95% confidence interval (CI) and classification accuracy rates of the blood values were noted in detail (Table-2).

Discussion

Abdominal pain is among the most common complaints of children, and constitutes approximately 10% of emergency room (ER) admissions. Discriminating abdominal pain requiring emergency surgery from the abdominal pain that does not require surgical intervention can be

particularly difficult in infants and toddlers. As this situation may cause unnecessary surgeries, it may also cause increase in morbidity and mortality by leading to delay in diagnosis. The fact that there are studies reporting that negative appendectomy are performed at rates ranging 5-40% explains how important it is to obtain the correct diagnosis.^{7,8}

The assessment and management of acute abdomen may vary according to the age and gender of patient. Although mostly detailed medical history and physical examinations are done, in cases requiring differential diagnosis, the use of laboratory and radiological investigations are inevitable. For children with abdominal pain, ML and FMF constitute a major part of the diseases, which are confused with appendicitis. FMF can be defined as an autosomal recessive disease and it typically presents with diffused abdominal pain attacks and fever episodes.³ Studies report that unnecessary appendectomies are performed at quite high rates in the children carrying FMF gene mutations.⁹⁻¹¹

Again, since ML patients present with the clinical

manifestations similar to appendicitis, it often causes confusion in the diagnosis of appendicitis.^{12,13} In our series, the diagnosis of appendicitis was confirmed pathologically in 137 of 143 patients who were operated with the pre-diagnosis of appendicitis while three patients were found to be compatible with ML, one with omental torsion and one with Meckel's diverticulitis among five patients in whom exploration resulted in the negative. We determined ML as the most common reason of negative exploration. Our series did not include any patient with FMF who were operated upon.

Since US does not contain ionizing radiation, it is one of our most commonly preferred methods for the differential diagnosis of acute abdomen with specificity ranging 68-90% in children.¹⁴ However, its likelihood of success may decline due to patient-associated causes, such as body mass index (BMI) and depending on the experience of the radiologist.¹⁵ The false positivity (FP) rate of US was reported as 20-44%.¹⁶ In the present study, US was determined to have a sensitivity of 91.25% and a specificity of 60% while its FP rate was very low (2.60%). This can be attributed to the fact that experienced radiologists performed all US examinations.

Blood cell analysis can reveal numerous diseases such as appendicitis, heavy metal poisoning, malaria, leukaemia, anaemia, syphilis, etc. Various studies indicate that high WBC count is associated predominantly with an inflamed appendix, thus a majority of cases show leukocytosis.^{17,18} WBCs are made up of neutrophil, monocyte, basophil, lymphocyte and eosinophil. CBCs revealing left shift are indicative of appendicitis.

WBC was reported to have a sensitivity of 67-80% and specificity 31.9-80% in various studies.^{8,18,19} There are also studies indicating that it shows the severity of appendicitis.⁵

In the present study, WBC was the most potent parameter with a classification accuracy rate of 74.2% and OR of 1.2 after US as well. Thus, the efficacies of other parameters could be assessed by taking US and WBC as reference.

MPV is associated with the function and activation of platelet and it increases depending on the increased production of platelets in infections and intense inflammation.^{4,20} Bilici et al. showed that the MPV level in the appendicitis group was significantly decreased compared to the control group in a paediatric group.²¹ However, Uyanik et al. presented that the MPV levels of paediatric patients were unpredictable for the usage of acute appendicitis diagnosis.²² In contrast, Narci et al. took the cut-off value as 7.87fL. The sensitivity, specificity

and AUC were calculated as 66%, 51% and 0.62. They demonstrated that the MPV in the appendicitis group was higher compared to the control group.²³ In addition, we reported MPV level significantly higher in the acute appendicitis group compared to the ML group. Makay et al. showed that MPV had a significantly severe drop during the attack period in FMF patients compared to non-attack period and healthy subjects.²⁴ Although MPV was found to be lower than normal values in the FMF group in the present study, no statistically significant difference could be detected among the ML and appendicitis groups.

Neutrophil has a pivotal role in the immune system. They are regarded as a powerful component in fighting infections and governing mast cells, epithelial cells and macrophages. The early stages of infectious diseases caused by bacteria and viruses show NLR changes.²⁵ There are numerous studies indicating that NLR is significant in the differential diagnosis of appendicitis compared to healthy volunteers when it is above 3.5.^{26,27} In recent years, a number of studies have shown that NLR works in determining the severity of appendicitis.^{28,29} The present study indicated that the NLR was useful in differentiating acute appendicitis. The reason for this is the fact that the drop of lymphocyte count was more pronounced in the appendicitis group in which the increase in neutrophil count was the highest. Similar to the present work, Kucuk et al. revealed that the NLR was effective in the differential diagnosis of appendicitis and FMF (sensitivity: 78%; specificity: 62%; AUC: 0.760).³⁰ This is the only study in the literature similar to our study.

The PLR is another tool to examine crucial inflammatory cases. As platelets are cells that have a certain effect on infections, changes in PLR level might play an important role in the diagnosis and/or differential diagnosis of appendicitis.²⁵ Yazar et al. found PLR effective in diagnosing acute appendicitis in pregnant women (at the cut-off value of >121.78 for PLR; sensitivity: 100%; specificity: 42.9%; and AUC: 0.712).²⁵ Also, Bekdas et al. showed that PLR was a parameter which could be used for discriminating simple/complex appendicitis (at the cut-off value of 195, sensitivity and specificity are 61.8% and 62.5%).⁴ In the present study, PLR was a useful parameter for differentiating appendicitis from FMF and ML.

Cases of neutrophilia indicating left shift are often related to lymphopenia, which are accompanied by monocytosis, a marker demonstrating acute inflammation.¹⁷ When our data was examined, appendicitis was detected to be the group in which neutrophil and monocyte increased mostly and lymphocyte decreased mostly. Therefore, LMR was determined to be highest in the FMF group while it

was found to be lowest in the appendicitis group. Compared to the ML and FMF groups, it was significantly lower for the appendicitis group. Although it had low sensitivity and specificity, it had a high classification accuracy rate (70.6%). However, since the AUC was quite low (0.259), it was not considered a potent parameter for differential diagnosis.

When NLR, WBC and PLR were positive, the classification accuracy rate was 76.4%. When WBC was combined with the PLR and NLR, they had a higher classification accuracy rate than their single effects in the differential diagnosis of appendicitis.

As encountered frequently while screening literature, healthy volunteers were not enrolled in the present study as the control group. On the contrary, patients with ML and FMF who presented with abdominal pain and included in the differential diagnosis of appendicitis most commonly were taken as the control group. MPV, NLR, and PLR were found to be potent at close rates to WBC and US, which are accepted as reference in the differential diagnosis of appendicitis. This makes the present study original in global literature.

Apart from being a retrospective study, the patients with acute appendicitis, FMF and ML, who had acute inflammation, were included. However, the most important limitation of the present study is examining the results of the blood taken without knowing the onset time of inflammation.

Conclusion

CBC was found to be a cost-effective and easily applicable parameter for critical diagnoses. NLR, MPV and PLR values obtained from proportioning CBC parameters are potent predictors for the differential diagnosis of appendicitis from FMF and ML, which are the diseases confused most commonly with appendicitis. LMR was found to be less powerful in this regard. The power of these parameters will increase when combined with physical examination, anamnesis and US.

Disclaimer: This study was presented as an oral presentation at the 35th Annual Congress of Turkish Associations of Paediatric Surgeon (TAPS), October 25-28, 2017, at Edirne, Turkey.

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