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MONOCYTE DISTRIBUTION WIDTH; CAN IT BE USED AS AN EARLY DIAGNOSIS MARKER IN CASES OF ACUTE COMPLICATED APPENDICITIS? A PRELIMINARY STUDY

MONOSİT DAĞILIM GENİŞLİĞİ AKUT KOMPLİKE APENDİSİT OLGULARINDA ERKEN TANI BELİRTECİ OLARAK KULLANILABİLİR Mİ? ÖN ÇALIŞMA

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ABSTRACT

AIM: The aim of this study was to investigate the effectiveness of monocyte distribution width in both the diagnosis of acute appendicitis (AA) and in differentiating between simple appendicitis (SA) and complicated appendicitis (CA).

MATERIAL AND METHOD: This study was conducted using data from 107 adult patients who underwent appendectomy. Demographic details, preoperative white blood cell (WBC) count, immature granulocyte count (IG) and percentage (IG %), monocyte distribution width (MDW), neutrophil-lymphocyte ratio (NLR) and pathology results were evaluated retrospectively. Patients were grouped as AA and normal appendix (NA) according to the pathology reports, and the AA cases were divided into SA and CA groups according to the intraoperative findings.

RESULTS: WBC, IG, IG%, NLR and MDW values were found to be statistically significant for the differentiation of acute appendicitis from normal appendicitis cases ($p < 0.05$). Of these parameters, the strongest parameter for the diagnosis of AA was NLR (sensitivity: 76%, specificity: 89%, $p< 0.001$). The IG value was found to be statistically significant in the diagnosis of complicated appendicitis cases ($p < 0.05$)

CONCLUSION: The MDW value is a fast, reliable and easily accessible parameter in the diagnosis of AA. However, although MDW values were found to be high in CA cases in the differentiation of SA and CA, they were not statistically significant. More comprehensive studies are needed for a clearer assessment.

Keywords: Acute appendicitis; complicated appendicitis, monocyte distribution width

ÖZET

AMAÇ: Bu çalışmanın amacı, apandisit (AA) tanısında ve ayrıca basit apandisit (SA) ile komplike apandisit (CA) arasında ayırıcı tanıda monosit dağılım genişliğinin etkinliğini araştırmaktı.

GEREÇ VE YÖNTEM: Bu çalışma, apandektomi yapılan 107 erişkin hastanın verileri kullanılarak gerçekleştirildi. Demografik detaylar, preoperatif beyaz kan hücresi (WBC) sayısı, inmatür granülosit sayısı (IG) ve yüzdesi (IG %), monosit dağılım genişliği (MDW), nötrofil-lenfosit oranı (NLR) ve patoloji sonuçları geriye dönük olarak değerlendirildi. Hastalar patoloji raporlarına göre AA ve normal apendiks (NA) olarak gruplandı ve AA olguları intraoperatif bulgulara göre SA ve CA gruplarına ayrıldı.

BULGULAR: Akut apandisit ile normal apandisit olgularını birbirinden ayırt etmede WBC, IG, IG%, NLR ve MDW değerleri istatiksel olarak anlamlı bulundu ($p < 0.05$). Bu parametreler içerisinde AA tanısı için en güçlü parametre ise NLR olduğu görüldü (sensitivitesi : 76%, spesifite : 89%, $p< 0.001$). Komplike apandisit olgularının tanısında ise IG değeri istatiksel olarak anlamlı bulundu($p < 0.05$)

SONUÇ: MDW, AA tanısında hızlı, güvenilir ve kolay ulaşılabilir bir parametredir. Ancak SA ile CA ayrımın da MDW değerleri CA olgularında yükseldiği görülse de istatiksel olarak anlamlı bulunmadı. Daha net bir değerlendirme için daha kapsamlı çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Akut apandisit; komplike apandisit, monosit dağılım genişliği

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INTRODUCTION

The appendix vermiformis (AV) is a narrow, blunt-ended tubular organ attached to the cecum. Inflammation of the AV is known as acute appendicitis, which is one of the most common inflammatory diseases of the gastrointestinal tract. Reduction in blood flow as a result of obstruction of the appendix lumen, mucosal ischemic damage, and infection due to bacterial growth play a role in the pathogenesis of acute appendicitis (1).

Despite the availability of several algorithms and grading systems for the diagnosis of appendicitis, which includes a history, physical examination, and laboratory results, appendicitis can still be easily overlooked (2).

In western countries, approximately 8% of the general population is at risk of having an appendectomy in their lifetime (3) . The majority of acute appendicitis cases are uncomplicated appendicitis. Complicated appendicitis (CA) is seen in approximately 20% to 30% of cases, while this rate rises to 50% in elderly patients (4, 5). Acute complicated appendicitis is a serious problem that increases the risk of morbidity and mortality in the postoperative period, prolongs hospital stay and increases medical costs (6). Therefore, early diagnosis and treatment of CA is critical (7).

Researchers have previously studied data such as NLR, platelet (PLT) value, mean platelet volume (MPV), platelet distribution width (PDW), red cell distribution width (RDW), IG, and IG percentage to assess the accuracy of the diagnosis of acute or complicated appendicitis (8-11).

A feasibility study recently conducted at a single academic center found that acute changes in monocyte size, referred to as the monocyte distribution width (MDW), best distinguished sepsis from other acute illnesses in the emergency department (e.g., compared to neutrophil volume changes), and that the combined performance of MDW and WBC for early sepsis detection was superior (12).

In the light of these studies to determine the severity of sepsis, the aim of this retrospective study was to evaluate whether MDW could play a role in the identification of patients with acute complicated appendicitis.

MATERIAL AND METHOD

The study included 107 adult patients who underwent appendectomy with a prediagnosis of acute appendicitis (AA) at xxx General Surgery Clinic between January 2019 and March 2020. Patients under the age of 18 years, pregnant women, and those with hematological comorbidities that may affect inflammatory markers were excluded from the study.

The demographic data, laboratory values and pathology results of the patients included in the study were retrieved from the hospital database records and analyzed. After a clinical history and abdominal examination, the complete blood count (CBC) of patients who presented at the Emergency Department with acute abdominal discomfort was assessed in patients with suspected AA. WBC, neutrophil, lymphocyte, and MDW levels were determined using an automated hematological analyzer (XN 3000; Sysmex Corp., Kobe, Japan) from blood samples drawn in the Emergency Department prior to surgery. The NLR, IG, IG percentage, and MDW values were derived using the CBC analysis results.

The patients in the research were classified into two groups based on their pathology reports: acute appendicitis and normal appendicitis (NA; negative appendectomy). Acute appendicitis patients were divided into two categories: simple appendicitis (SA) and complicated appendicitis (CA) (gangrenous, perforated and abscess). Preoperative laboratory results and demographic data were statistically evaluated and compared.

Statistical Analysis

Data obtained in the study were analyzed statistically using IBM SPSS Statistics for Windows, version 25.0 software (IBM Corp., Armonk, N.Y., USA). The normality of the distribution of numerical variables was analyzed with the Shapiro-Wilk test. Normally distributed numerical variables were given as mean ± standard deviation (SD) values and were analyzed with the Student's t-test. Non-normally distributed numerical variables were given as median (minimum-maximum) values and were analyzed with the Mann-Whitney U test. Categorical variables were expressed as frequency (n) and percentage (%) and were assessed using the Chi-square test. Receiver operating characteristic (ROC) curves were created to determine the optimal cut-off value of continuous variables. A value of $p<0.05$ was considered statistically significant.

RESULTS

The demographic data, laboratory findings, and pathology results of the whole study group are summarized in **Table 1**. The median age of the study group was 33 (17-80) years and 59.8% (n=64) of the patients were male. Pathological examinations revealed that 17.8% (n=19) of the patients who were operated on with the diagnosis of acute appendicitis had normal appendix. Of the 88 patients with pathologically proven acute appendicitis, 64 were evaluated as simple appendicitis and 24 as complicated appendicitis.

The results and comparisons between the acute appendicitis group and the normal appendix group are shown in **Table 2.** The male ratio was significantly higher in the AA group ($p= 0.006$). In addition, higher WBC, IG , IG %, MDW, and NLR values were determined in the AA group than in the normal appendix group ($p= 0.001$, $p= 0.008$, $p= 0.028$, $p= 0.005$, and $p<0.001$ respectively).

The results and comparisons between the SA group and the CA group are presented in **Table 3.** The patients in the CA group were significantly older (41.5 years vs 32 years, $p= 0.019$). From the laboratory findings, only the IG significantly differed between the groups and was

higher in the CA group (p= 0.045).

The ROC analyses of the predictors for AA and CA are shown in **Table 4 and Table 5.** All parameters were significantly able to predict AA and NLR was determined to be better than the other parameters with a cut-off value of 4.37 (AUC=0.873, sensitivity: 76%, specificity: 89%, p<0.001). The ability of IG to differentiate CA from SA was significant with a cut-off value of 0.07 (AUC=0.639, sensitivity: 58%, specificity: 70%, p<0.046).

Table 1.Demographic data, laboratory findings, and pathology results of the whole study group

	Study group (n=107)
Age (years), median (min.-max.)	33 (17-80)
Gender (male), n (%)	64 (59.8)
WBC, median (min.-max.)	14.92 (5.14-35.00)
IG, median (min.-max.)	0.06 (0.00-0.77)
IG %, median (min.-max.)	0.40 (0.00-2.20)
MDW, mean ± SD	739.38 ± 83.91
NLR, median (min.-max.)	6.25 (1.02-38.58)
Pathology	
Normal appendix, n (%)	19 (17.8)
Acuteappendicitis, n (%)	88 (82.2)
Simple appendicitis, n (%)	64 (59.8)
Complicatedappendicitis, n (%)	24 (22.4)

Min: Minimum, Max: Maximum, SD: Standard deviation, WBC: White blood cell; IG: Immature granulocytes; IG%: Immature granulocytes percentage; MDW:Monocyte distribution width; NLR: Neutrophil-to-lymphocyte ratio

Table 2.Results and comparisons of the demographic data and laboratory findings of the acute appendicitis group and the normal appendix group.

	Acute appendicitis (n=88)	Normal appendix (n= 19)	P value
Age (years), median (min.-max.)	33.5 (18-80)	29 (17-67)	0.613
Gender (male), n (%)	58 (65.9)	6 (31.6)	**0.006***
WBC, median (min.-max.)	15.52 (7.48-35.00)	12.03 (5.14-18.80)	**0.001***
IG, median (min.-max.)	0.06 (0.01-0.77)	0.05 (0.00-0.14)	**0.008***
IG %, median (min.-max.)	0.40 (0.10-2.20)	0.40 (0.00-0.90)	**0.028***
MDW, mean ± SD	749.73 ± 82.87	691.42 ± 72.92	**0.005***
NLR, median (min.-max.)	7.21 (1.43-38.58)	2.53 (1.02-6.45)	**<0.001***

Min: Minimum, Max: Maximum, SD: Standard deviation, WBC: White blood cell; IG: Immature granulocytes; IG%: Immature granulocytes percentage; MDW:Monocyte distribution width; *: Statistically significant

Table 3.Results and comparisons of the demographic data and laboratory findings of the simple appendicitis group and the complicated appendicitis group.

	Simple appendicitis (n=64)	Complicated appendicitis (n=24)	P value
Age (years), median (min.-max.)	32 (18-60)	41.5 (22-80)	**0.019***
Gender (male), n (%)	43 (67.2)	15 (62.5)	0.679
WBC, median (min.-max.)	15.30 (7.48-25.72)	16.60 (7.91-35.00)	0.097
IG, median (min.-max.)	0.06 (0.01-0.15)	0.08 (0.02-0.77)	**0.045***
IG %, median (min.-max.)	0.40 (0.10-1.00)	0.50 (0.20-2.20)	0.064
MDW, mean ± SD	722.28 ± 86.05	765.62 ± 73.04	0.273
NLR, median (min.-max.)	6.61 (1.43-38.58)	8.56 (2.39-27.34)	0.062

Min: Minimum, Max: Maximum, SD: Standard deviation, WBC: White blood cell; IG: Immature granulocytes; IG %: Immature granulocytes percentage; MDW:Monocyte distribution width; *: Statistically significant

Table 4. The ROC analysis of the predictors for acute appendicitis

	AUC	95% confidence interval		Cut-offvalue	Sensitivity (%)	Specificity (%)	P value
		Lower bound	Upper bound				
WBC	0.735	0.609	0.862	14.855	0.580	0.789	0.001
IG	0.694	0.554	0.835	0.055	0.648	0.684	0.008
IG %	0.656	0.517	0.796	0.450	0.386	0.842	0.033
MDW	0.706	0.592	0.820	706.500	0.727	0.789	0.005
NLR	0.873	0.801	0.946	4.373	0.761	0.895	<0.001

ROC: Receiver operating characteristics; AUC: Area under curve; WBC: White blood cell; IG: Immature granulocytes; IG %: Immature granulocytes percentage; MDW:Monocyte distribution width

Table 5. The ROC analysis of the predictor for complicated appendicitis

	AUC	95% confidence interval		Cut-off value	Sensitivity (%)	Specificity (%)	P value
		Lower bound	Upper bound				
IG	0.639	0.495	0.783	0.075	0.583	0.703	0.046

ROC: Receiver operating characteristics; AUC: Area under curve; IG: Immature granulocytes

DISCUSSION

An accurate acute appendicitis diagnosis is critical not only for lowering NA rates, but also for distinguishing severe appendicitis cases such as perforated appendicitis from uncomplicated appendicitis. Despite advancements in diagnostic methods and treatment, substantial incidence of NA and perforation are still observed today (13-36 %, 12-21 %, respectively). Perforation rates are as high as 50% in older individuals, especially (13-15).

Patients with CA, such as perforation, have higher morbidity and mortality rates, longer hospital stays, and higher medical expenditure. Therefore, new biomarkers are required to lower the risk of both NA and CA. CRP is a well-known biomarker for predicting CA because the level rises 8-12 hours after the commencement of the inflammatory process and continues to rise for the next 24-48 hours. According to Moon et al., CRP is an independent predictor of CA (16). Abdelhalim et al. investigated the predictive value of combining WBC count, CRP, and bilirubin as biomarkers, and discovered that this combination had high specificity (95%) for the diagnosis of acute and complex appendicitis [17]. WBC is a biomarker frequently utilized in the diagnosis of acute appendicitis. In a clinical study by Demircan et al., it was stated that WBC, other inflammatory markers, and abdominal ultrasonography and computed tomography of the abdomen were supportive tests in the diagnosis of acute appendicitis (18). Ertekin et al. showed that the WBC level is high in patients with acute appendicitis and WBC sensitivity was reported as 70% and specificity as 60 % (19). In this study, WBC values were found to be high in AA patients with sensitivity of 58 % and specificity of 78 %.

The physiological response of circulating leukocytes under stress is generally an increase in neutrophil count and a decrease in lymphocyte count. Therefore, the NLR of these 2 subgroups is used as an inflammation parameter. In a study by Kahramanca et al., NLR was determined to be a useful parameter in diagnosing AA and for differentiating between SA and CA (20). In the current study, NLR was found to be the strongest parameter in diagnosing AA.

As a result of technological developments in automated hematological analyzers, it is now feasible to identify the proportion and number of IG, and recent studies have demonstrated that IG may be employed as an efficient inflammatory marker (21, 22). However, in a trial with 403 patients, Park et al. discovered that the sensitivity of IG% was insufficient for the diagnosis of AA and did not give any significant advantage when compared to other inflammatory markers (23). In contrast, another investigation comprising 438 patients reported that the IG value was a quick, easy-to-access, and reliable measure in both the diagnosis of AA and the differentiation of SA from CA (11). In the current study, IG % and IG values were determined to be statistically significant in the diagnosis of AA. The IG value was likewise discovered to be the sole statistically significant measure in differentiating between SA and CA.

Neutrophils and monocytes in the plasma are the initial line of defence against pathogenic microorganisms. Recent research has demonstrated that increased immune cell volume can be used to diagnose sepsis. Crouser et al. demonstrated that combining MDW and WBC might be utilized to diagnose sepsis (24). In another study, Crouser et al. stated that MDW might be useful in the early detection of sepsis in the Emergency Department (25). According to a recent study by Ognibene et al., MDW might be utilized

as an indication of sepsis in COVID-19 patients (26). The MDW values were shown to be statistically significant in diagnosing AA in the current study, and although MDW values were greater in CA cases than in SA, the difference was not statistically significant.

CONCLUSION

In conclusion, WBC, NLR, IG, IG%, and MDW levels are criteria that can be utilized to diagnose AA. The IG value was shown to be more beneficial than other criteria in the diagnosis of CA. However, this was preliminary research testing the use of MDW value in the diagnosis of CA patients, and there is a need for further studies with larger patient populations to provide a more accurate assessment.

STATEMENT OF AUTHOR CONTRIBUTIONS

KK, AD, AŞ : **Work management, article writing, background assessment, literature review, final decision** MS, CE, EE: **Design, article writing, literature review** YMB, MŞ, MRP: **Statistics, literature review**

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