



Assessment of Monocyte/HDL Ratio in Patients with Acute Appendicitis

Akut Apandisitli Hastalarda Monosit/HDL Oranının Değerlendirilmesi

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ABSTRACT

Aim: In patients with acute appendicitis (AA), the number of monocytes increase and the level of high-density lipoprotein cholesterol (HDL-C) decrease. The monocyte/HDL-C ratio (MHR) has recently been used as a diagnostic and prognostic marker for acute inflammation. As far as we research in the literatures, there is no information about the use or alteration of MHR in patients with AA. The aim of this study was to investigate the MHR change in patients with AA and its utility for this disease.

Methods: This cross-sectional study includes 206 patients with AA and 57 healthy controls that are similar in age and sex. Serum lipid panel was measured in all patients in addition to routine history, physical examination and laboratory evaluations. Patients were divided into two groups with and without AA and all data were compared.

Results: MHR was significantly higher in patients with AA (17.5 ± 9.9 vs 8.5 ± 1.6 and $p < 0.001$). Perforation was detected in 32 (15.5%) patients with AA. MHR was significantly higher in patients with perforation than non-perforated patients (16.1 ± 8.46 vs 23.5 ± 9.34 and $p < 0.001$). Laboratory data showed that white blood cell count, monocyte, lymphocyte, neutrophil, triglyceride and neutrophil/lymphocyte ratio (NLR) levels were higher in patients with AA; serum HDL cholesterol levels were lower ($p < 0.05$ for each-one). In logistic regression analysis, it was determined that MHR and NLR values independently determined AA patients. The area under the curve was most for MHR and the area under the curve was 0.865 and 0.780 for MHR and NLR, respectively. In this analysis, when the cut-off value for MHR was taken as 10, it was found that it detected the patients with AA with a sensitivity of 80.4% and a specificity of 81.8%.

Conclusion: In our study, it was found for the first time that MHR value was significantly increased in patients with AA. In addition to the classical diagnostic examinations in patients presenting to the emergency department with the diagnosis of AA; MHR can also be used in diagnostic approach as a simple, easily accessible, inexpensive and objective parameter.

Keywords: Acute appendicitis, monocyte/HDL ratio, emergency department

ÖZ

Amaç: Akut apandisit (AA) hastalarında monosit sayısı artar ve yüksek-dansiteli lipoproteyin kolesterol düzeyi (HDL) ise azalmaktadır. Monosit/HDL-C oranı (MHR) son günlerde akut inflamasyon durumunda tanılal ve prognostik bir belirleyici olarak kullanılmaktadır. Literatürde araştırdığımız kadari ile AA hastalarında MHR değişimi veya kullanımı ile ilgili bilgi yoktur. Bu çalışmada AA hastalarında MHR değişimini ve bunun bu hastalık için kullanılabilirliğinin araştırılması amaçlandı.

Yöntem: Bu cross-sectional çalışmaya AA olan 206 hasta ve yaş ile cinsiyet olarak benzer AA olmayan 57 kontrol alındı. Tüm hastalara rutin anamnez, fizik muayene ve laboratuvar değerlendirmelerine ek olarak serum lipid paneli ölçüldü. Hastalar AA olan ve olmayan olarak 2 gruba ayrılarak tüm veriler karşılaştırıldı.

Bulgular: AA olan hastalarda MHR anlamlı olarak yüksekti ($17,5 \pm 9,9$ ve $8,53 \pm 1,56$ ve $p < 0,001$). Otuz iki (%15,5) AA hastasında perforasyon saptandı. Perforasyon olan hastalarda perfore olmayanlara göre de MHR anlamlı olarak yüksekti ($16,1 \pm 8,46$ ve $23,5 \pm 9,34$ ve $p < 0,001$). Laboratuvar verilerinden WBC sayısı, monosit, lenfosit ve nötrofil, trigliseride ve nötrofil/lenfosit ratio (NLR) düzeylerinin AA olan hastalarda yüksek; serum HDL kolesterol düzeyi ise düşüktü ($p < 0,05$ her biri için). Lojistik regresyon analizinde, MHR ve NLR değerlerinin AA olan hastaları bağımsız olarak belirlediği saptandı. Buna analize göre MHR ve NLR değerlerindeki her 0,2 mm artışın AA olma riskini sırası ile 3.8 ve 1.4 kat artırdığı saptandı. Ayrıca



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AA olan hastaları belirlenmesi için ROC eğri analizi yapıldı; eğri altında kalan alan en fazla MHR olduğu ve eğri altında kalan alanın MHR ve NLR için sırası ile 0,865 ve 0,780 olduğu bulundu. Bu analizde MHR için sınır değeri 10 olarak alındığında, AA olan hastaları %80,4 duyarlılık ve %81,8 özgüllük ile belirlendiği tespit edildi.

Sonuç: Çalışmamızda ilk kez AA hastalarında MHR değerinin anlamlı olarak arttığı bulundu. Acil servise AA ön tanısı ile gelen hastalarda klasik tanısal incelemelere ek olarak; basit, kolay ulaşılabilen, ucuz ve objektif bir parametre olarak MHR da tanısal yaklaşımda kullanılabilir.

Anahtar Kelimeler: Akut apandisit, monosit/HDL oranı, acil servis

Introduction

Acute appendicitis (AA) is the most common cause of acute abdomen in all age groups who present to the emergency department. Acute inflammation increases with the disease in the course; oxidative stress, endothelial dysfunction, and increased local and systemic inflammatory biomarkers.^{1,2} The number of monocytes from the white blood cell (WBC) and its subtypes is also increased.^{2,3,4} AA is a disease that starts locally and increases systemically with inflammation. Patients with AA have an increase in WBC, lymphocyte, neutrophil and monocyte counts.^{2,3,5} The increase of lymphocyte percent is higher than neutrophil increase and therefore studies have shown that neutrophil/lymphocyte ratio (NLR) is higher in patients with AA.^{2,3,4,5,6,7,8,9} It has been reported that NLR can be used for diagnostic purposes in patients with AA.^{6,7,8,9} High density lipoprotein (HDL) cholesterol has anti-inflammatory and anti-oxidant effects, and serum HDL cholesterol decreases in many systemic inflammations including myocardial infarction.^{5,10}

Systemic inflammation in AA leads to an increase in inflammation and a decrease in HDL cholesterol levels and activity.^{11,12} Increased monocyte and decreased HDL cholesterol levels and the ratio of these two parameters to monocyte/HDL ratio (MHR) have been shown in the literature in many inflammatory diseases.^{10,13,14,15,16,17,18,19,20,21} It has also been found that this parameter, such as NLR, is a diagnostic approach to many inflammatory diseases, as well as the severity of inflammation and a prognostic marker.^{10,13,14,15,16,17,18,19,20,21,22,23} In patients with AA, the number of monocytes increases and the level of high-density lipoprotein cholesterol (HDL-C) decrease. The monocyte/HDL-C ratio (MHR) has recently been used as a diagnostic and prognostic marker for acute inflammation. To the best of our knowledge, there is no information about the MHR change or diagnostic use in AA patients and whether it is a prognostic marker. We have hypothesized that MHR will increase with increasing monocyte and decreasing HDL cholesterol levels in AA patients.

Therefore, the aim of this study was to investigate the MHR change in AA patients and its use for this disease.

Materials and Methods

Study Populations

This cross-sectional study included 263 patients who presented to our emergency department with abdominal pain. A total of 206 patients (mean age: 35.2±13.5 years, male/female: 129/77) who were operated for AA and diagnosed as AA in the pathological diagnosis, and 57 controls who were discharged from the emergency department with similar abdominal pain in age and sex but not diagnosed with AA (mean age: 50.2±10.1 years, male/female: 31/26). The patients who were screened to the control group were excluded from the study if they did not apply to emergency or general surgery clinics with abdominal pain for at least 1 month after discharge from the emergency department. In patients with a pre-diagnosis of AA, 14 patients whose pathological diagnosis was not associated with AA were excluded from the study. Those with active infection, recent acute coronary syndrome, secondary or malignant hypertension, pulmonary HT, abdominal aneurysm and dissection, congestive heart failure, cerebrovascular disease, moderate-severe heart valve disease, inflammatory diseases, hematological diseases, cancer and thyroid dysfunction, Moderate-severe hepatic and renal failure was excluded from the study due to the fact that MHR could increase. In addition, patients <18 years of age, pregnancy or suspicion of pregnancy, <18 years of age and who did not accept the study were excluded from the study. The study was approved by the regional ethics committee, all patients included in the study were informed about the study and a revised consent form was obtained.

Firstly, a detailed history was taken and physical examinations of all patients were performed. Demographic characteristics and clinical parameters of the all patients were recorded. Height and weight were measured and body mass index was calculated. AA was initially diagnosed clinically. In addition, the ALVARADO and RIPASA scoring systems were used for all patients in the emergency department.^{24,25} However, ultrasound (US) and computerized tomography (CT) support was also obtained from radiological evaluations in patients who could not be diagnosed clinically. However, these two examinations were not evaluated because they were not present in all cases.

Biochemical Measurements

Venous blood samples were obtained at polyclinic admission. Samples were taken from cubital vein into blood tubes. Blood counts were measured by a Sysmex K-1000 (Block Scientific, Bohemia, New York) auto analyzer within 5 min of sampling. Serum glucose, blood urea nitrogen, creatinine, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein (HDL) cholesterol, triglyceride, hs-CRP and uric acid concentrations were measured with an automated chemistry analyzer (Abbott Aeroset, Minnesota, USA) using commercial kits (Abbott).

Statistical Analysis

All analyzes were performed using SPSS 22.0 (Chicago, IL, USA) statistical software package. Kolmogorov-Smirnov test was used to determine whether the distribution of continuous variables was normal. Continuous variables in the group data were expressed as mean \pm standard deviation. Categorical variables were expressed as numbers and percentages. Student's t-test was used for the comparison of continuous variables between groups. However, Mann-Whitney U test was used for the evaluation of non-normal distribution parameters. Chi-square test was used to

compare categorical variables. Logistic regression analysis was used to determine the parameters that independently identified patients with AA. In addition, ROC curve analysis was performed for MHR to identify patients with AA. Multivariate linear regression analysis was performed for the association of MHR with Alvarado and RIPASA. Statistical significance was accepted if $p < 0.05$.

Results

Mean, median, minimum and maximum MHR values of all patients with AA were 17.5 ± 9.9 , 15.6, 4.61 and 47.5 respectively. The mean, median, minimum and maximum MHR values of the non-AA control group were 8.53 ± 1.56 , 8.78, 4.61 and 10.9 respectively. The study population was divided into two groups with and without AA and all parameters were compared. Thirty-two (15.5%) of the patients with AA included in the study had perforation. Demographic, clinical and laboratory findings of the study groups were compared. When the demographic and clinical data of both groups were examined, all demographic and clinical parameters were found to be similar between the two groups (Table 1). Laboratory data showed that WBC

Table 1. Demographic, clinic and laboratory findings in patients with acute appendicitis and controls

	Acute appendicitis n=206	Controls n=57	P
Age (year)	35.2 \pm 13.5	34.3 \pm 10.2	0.629
Gender (male)	129	31	0.202
Body mass index (kg/m ²)	25.1 \pm 2.8	25.0 \pm 3.1	0.987
Hospitalization day	3.27 \pm 1.81	-	-
ALVARADO	7.31 \pm 2.23	-	-
RIPASA	10.01 \pm 2.96	-	-
White blood cell count ()	13.5 \pm 6.5	8.04 \pm 1.45	<0.001
Red blood cell count	4.76 \pm 0.60	4.63 \pm 0.60	0.220
Hemoglobin	14.8 \pm 2.7	13.2 \pm 2.1	0.265
Platelet ($\times 10^9/L$)	252 \pm 81	247 \pm 99	0.820
Monocyte ($\times 10^9/L$)	661 \pm 228	402 \pm 72	0.001
Lymphocyte ($10^3/\mu L$)	1.74 \pm 0.98	2.11 \pm 0.62	0.465
Neutrophil ($10^3/\mu L$)	9.3 \pm 4.7	3.6 \pm 1.1	0.001
Mean platelet volume (fL)	9.21 \pm 1.38	8.42 \pm 0.97	0.413
Total Cholesterol (mg/dL)	203 \pm 41	198 \pm 44	0.392
LDL Cholesterol (mg/dL)	135 \pm 35	133 \pm 33	0.638
HDL Cholesterol (mg/dL)	41.4 \pm 6.23	48.3 \pm 1.68	<0.001
Triglycerid (mg/dL)	200 \pm 101	159 \pm 77	0.005
Neutrophil/ Lymphocyte ratio	9.1 \pm 9.1	1.8 \pm 0.67	<0.001
Monocyte/HDL ratio	17.5 \pm 9.9	8.53 \pm 1.56	<0.001

HDL: High density lipoprotein, LDL: Low density lipoprotein

counts, monocyte, lymphocyte and neutrophil, triglyceride, NLR and MHR levels were higher in patients with AA; serum HDL cholesterol level was low (Table 1). Other laboratory parameters were similar between the two groups (Table 1). Logistic regression analysis was performed to determine the most effective parameters determining the presence of AA among the different parameters in AA and non-AA patient groups. Among these parameters, only MHR and NLR values independently determined patients with AA (Table 2). According to this analysis, each 0.2 mm increase in MHR and NLR values increased the risk of AA to 3.8 and 1.4 times, respectively (Table 2). Also in the linear regression analysis, only MHR was independently associated with the Alvarado and RIPASA scores of the diagnostic scores for AA ($p < 0.001$ and $\beta = 0.420$ and $p < 0.001$ and $\beta = 0.382$). In the same analysis, NLR and Alvarado and RIPASA scores were not independently related. MHR was significantly higher in patients with perforated AA than in non-perforated AA group (16.1 ± 8.46 vs. 23.5 ± 9.34 and $p < 0.001$).

ROC curve analysis was also performed to identify patients with AA; the parameters under the curve > 0.700 are shown in Table 3. The area under the ROC curve was found to be the most MHR and the area under the curve was 0.865 and 0.780 for MHR and NLR, respectively. In this analysis, when the cut-off value for MHR was taken as 10, it was found that it identified patients with AA with a sensitivity of 80.4% and a specificity of 81.8%. When the cut-off value for NLR was taken as 12.4, it was found that it determined the patients with AA with 71.2% sensitivity and 70.4% specificity.

Discussion

The most important finding of our study was that the MHR value in patients with AA was higher than in non-AA controls. According to our research, this is the first study to demonstrate increased MHR in patients with AA. Another important finding is that in patients with AA, MHR is more

significantly associated with ALVARADO and RIPASA scores than AA. When the MHR cut-off value is taken as 10, it determined the patients with advanced AA with acceptable sensitivity and specificity. In addition, MHR was significantly higher in AA patients than in non-perforated patients.

In inflammatory diseases, elevated local and systemic inflammation biomarkers and their amount are used both in the diagnosis and prognosis of these diseases. WBC and its subtypes increase in diseases leading to acute local and systemic infection and inflammation. They cause an increase in the activation of inflammatory cells in these cells, and then increase the activity of each other through a vicious cycle. With the diagnosis and subsequent treatment, this inflammatory cell and its markers decrease and change in time depending on the course of the disease. Many recent studies have shown that NLR is increased in cardiovascular and systemic diseases such as atrial fibrillation, diabetes mellitus, atherosclerosis, and myocardial infarction.^{26,27,28} A similar situation has been shown in several studies involving patients with AA.^{6,7,8,9} In patients with AA, NLR is significantly more pronounced in this disease than lymphocyte count is higher than the neutrophil count, but both cell groups are significantly increased.^{2,3,4} The results of NLR in patients with AA were supportive of previous studies in the literature. It was once again shown that NLR was significantly increased in patients with AA and that it could be used as an auxiliary laboratory parameter in the diagnosis of AA. However, diagnostic strength for AA was lower than MHR.

Another increasing blood cell in patients with AA was monocytes.^{2,3,4} Monocytes are indicators of inflammatory reactions because monocytes are responsible for the secretion of proinflammatory and pro-oxidant cytokines.²

HDL cholesterol reduces the accumulation of macrophages by sweat interaction with monocytes, increases NO synthase from the endothelium, and inhibits monocyte transmission

Table 2. According to multivariate regression analysis, independent risk factors for occurrence of acute appendicitis

	Odds ratio	95% Confidence interval	p
Monocyte/HDL ratio (each 0.2)	3.802	1.468-9.844	0.006
Neutrophil/ Lymphocyte ratio (each 0.2)	1.408	1.072-1.849	0.014

HDL: High density lipoprotein

Table 3. ROC curve analysis of monocyte/HDL and neutrophil/lymphocyte ratios for acute appendicitis

Variable	Area under ROC curve	p	Cut-off value	Sensitivity	Specificity
Monocyte/HDL ratio	0.865 (0.823-0.907)	< 0.001	10.0	80.4%	81.8%
Neutrophil/Lymphocyte ratio	0.780 (0.700-0.859)	< 0.001	12.4	71.2%	70.4%

HDL: High density lipoprotein, ROC: Receiver operating characteristic

from the endothelium and has an anti-inflammatory and anti-oxidant effect.⁵ Unfortunately, although the exact cause is unknown, HDL cholesterol levels and activity are reduced in inflammatory diseases.^{5,10} This is the case in patients with AA and HDL cholesterol levels decrease.^{11,12} In our study, HDL cholesterol decreased, while triglyceride level increased. Reduction of HDL cholesterol in inflammation as well as the reduction of both inflammation and cytokines synthesis from the liver, HDL can be used indirectly to suppress inflammation. MHR is a recently introduced parameter that can be measured simply by correlating inflammation and oxidative stress in the body.^{10,13,14,15,16,17,18,19,20,21,29} It is also a prognostic parameter.^{16,20,22,23} Because of this condition, a lot of studies have been made on MHR in acute coronary syndrome, stroke, hypertension, renal failure, heart failure, infective endocarditis, obstructive sleep apnea, atherosclerotic processes, coronary artery disease, myocardial infarction, cardiovascular prognosis, but MHR has not been studied in AA.¹⁶

However, AA also monocyte and HDL are inversely changing and it is evident that there may be an increase in MHR. For the first time in our study, MHR is more clearly diagnosed by MHR than both WBC and related blood cells and NLR. When the MHR is taken as a cut-off value of >10 for the diagnosis of AA, it makes the diagnosis of AA with acceptable sensitivity and specificity. In addition, every 0.2 unit increase in MHR increases the risk of AA being 3.8 times.

Traditionally, AA is diagnosed clinically. However, in many studies, some formulas have been developed for difficult cases and scenarios.³⁰ Some surgeons use scoring systems such as Alvarado and RIPASA.^{24,25} In addition, US and CT support is also support is also obtained from routine radiological evaluations.³¹ The fact that CT expose ionizing radiation and is expensive, and US is operator dependent, are the major disadvantage of radiological evaluations. Therefore, most surgeons are currently using anamnesis, physical examination, laboratory results and clinical scoring systems. According to the results of our study, WBC, NLR and MHR can be used in the emergency department in the diagnosis of AA.

In patients with AA, perforation is in the range of 18-34%.³² Early diagnosis is important in this condition, which may cause mortality, especially in the elderly.³³ Both total WBC count and NLR have been significantly increased in patients with perforated AA compared to non-perforated patients.^{3,34,35} Similarly, in our study, MHR was also increased in patients with perforated AA.

Study Limitations

In this study, MHR was studied cross-sectionally in patients with AA. We included a relatively small number of patients,

but showed that MHR was significantly increased in patients with AA. The study could have been more meaningful if it was performed prospectively and with more patients. In our study, due to the first use of MHR, there were no limit values in previous studies. Therefore, it should be supported by more randomized, multicenter studies involving different patients. US and CT imaging methods are used in the diagnosis of AA.⁸ However, we did not evaluate this technique and its results in our study due to the absence of these two examinations to all patients in our study. In addition, no correlation was found between CT and US findings and MHR.

Conclusion

As a result of our study, it was concluded that the ratio of HDL cholesterol levels, WBC parameters, HDL cholesterol levels are simple, inexpensive and objective MHR values in patients diagnosed with AA in Emergency department as an adjunct to other diagnostic methods in the diagnosis of AA and the severity of the disease. However, our study was the first to evaluate MHR in patients with AA. Therefore, the data in our study should be supported by new and more multicenter studies.

Ethics

Ethics Committee Approval: Adana City Training and Research Hospital, Clinical Research Ethics Committee (24.04.2019).

Informed Consent: All patients included in the study were informed about the study and a revised consent form was obtained.

Peer-review: Internally and externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: A.K., Concept: A.K., H.E.S., M.K., Design: A.K., H.E.S., M.K., Data Collection or Processing: A.K., H.E.S., M.K., Analysis or Interpretation: M.K., A.K., Literature Search: A.K., M.K., Writing: A.K.

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