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Original Article

Can monocyte to HDL ratio be used as an inflammatory marker in children with familial mediterranean fever?

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Abstract

Aim: Familial Mediterranean fever (FMF); is an auto-inflammatory disease characterized by recurrent fever attacks. Inflammation continues even in the attack-free period. Monocyte to high-density lipoprotein cholesterol (HDL-C) ratio (MHR) is an inflammatory marker that has recently begun to use. The aim of the study was to evaluate the relationship between MHR and FMF in children.

Material and Methods: Sixty-two children with FMF in the attack-free period and 60-age and sex-matched- healthy controls included in the study. Patients divided into subgroups according to their gene mutation type. Monocyte count and HDL-C levels retrieved from medical records of patients and MHR were calculated from these data.

Results: The MHR of individuals were close to each other and there was no statistically significant difference between them (p>0.05). Twenty-four of the patients had heterozygous, 4 had homozygous, 11 had a compound and 21 had negative mutations. Two of the patients had no mutation analysis. There was no significant difference between these four groups according to MHR (p=0.348). However, MHR revealed a positive correlation with fibrinogen (r=0.604, p<0.005, n=24), serum amyloid A (r=0.437, p=0.005, n=39), C-reactive protein (r=0.277, p=0.005, n=101), and erythrocyte sedimentation rate (r=0.404, p<0.001, n=104).

Conclusion: As a result, we showed MHR was not different from healthy controls in FMF patients. Contrary to what is claimed, the use of MHR as an inflammatory marker in FMF is doubtful.

Keywords: Monocyte hdl ratio; familial mediterranean fever; inflammation marker.

INTRODUCTION

Familial Mediterranean fever (FMF) is a hereditary autosomal recessive auto- inflammatory disease with recurrent fever attacks, arthritis, polyserositis and abdominal pain. FMF gene (MEFV) locates on the short arm of chromosome 16 and encodes pyrin/marenostrin (1). Pyrin protein is expressed by many cells, which plays important roles in the suppression of inflammation and apoptosis. In case of mutation of this protein, inflammation cannot be suppressed (2). Inflammatory episodes cause migration of neutrophils and other cytokines into the serosal regions (3). The levels of cytokines such as IL-6, IL-1Band sIL-2R, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), serum amyloid A (SAA), and fibrinogen increases, during the FMF attacks (4). Most studies have shown that subclinical inflammation persists even in the attack-free period (5-8).

Monocytes are the parts of the innate immune system that constitute 3-8% of circulating leukocytes. Pro-inflammatory and pro-oxidant cytokines secreted by monocytes and macrophages in inflammatory reactions. Macrophages, which are the circulating forms of monocytes, play a role in the inflammation. The overactive activation of monocytes causes the diseases such as atherosclerosis, arthritis, and multiple sclerosis, especially affecting platelets and endothelial cells (9-11). Recently it has been claimed that HDL-C has anti-inflammatory and anti-oxidant effects, as well as monocyte activation and suppressor effects on the differentiation and proliferation of progenitor cells (12,13). The monocyte count to HDL-C ratio (MHR) is the most recent indicator for morbidity and mortality in chronic inflammatory conditions such as cardiovascular disease, abdominal aortic aneurysm, chronic kidney disease, metabolic syndromes, hypertension, and intracerebral hemorrhage (14-20).

Several studies have aimed to discover new markers to determine subclinical inflammation in FMF patients such as neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), mean platelet volume (MPV) and

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red cell distribution width (RDW) (6-8). The monocyte to high-density lipoprotein cholesterol (HDL-C) ratio (MHR) has recently emerged as an indicator of inflammation as mentioned above. To the best of our knowledge, no study has yet examined the association between FMF and the MHR. Thus, we aimed to investigate the relationship between MHR and FMF in children.

MATERIAL and METHODS

This retrospective, cross-sectional study conducted between January 2016 and January 2017. One hundred twenty two pediatric patients (62 FMF patients and 60 healthy controls) were included. The information about patients obtained from their hospital records. FMF diagnosis based onto Tel Hashomer criteria (21) and all study groups was in attack-free period. The attack-free period was defined as no symptoms for at least 2 weeks after the last FMF attack and the acute phase reactants were normal (22). All patients prescribed colchicine daily. Age and gender matched healthy subjects were chosen from our healthy children outpatient clinic as control group. Patients who has chronic and other diseases excluded from the study.

Patients age, sex, white blood cell counts (WBC), high-density lipoprotein (HDL) levels, C-reactive protein (CRP) levels, and erythrocyte sedimentation rate (ESR), mutation type, serum amyloid-A (SAA) levels were obtained from hospital records. The MHR calculated by dividing the absolute monocyte count to HDL. PLR was calculated by dividing the platelet to lymphocyte count, and NLR was calculated by dividing the neutrophil to lymphocyte count. MHR and other laboratory results compared between groups.

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Sütçü İmam University Ethics Committee.

Statistical Analysis

All statistical analyses were performed using the SPSS version 14 (SPSS Inc., Chicago, IL, USA) software package. Statistical significance was set to a two-sided p-value ≤0.05. Categoric variables were expressed as number and percentage while continuous variables as mean ± standard deviation (SD) or median and interquartile range, depending on their normality of distribution. The independent sample t-test and Mann–Whitney U test were used to compare the groups' means. The Chi square test was used to compare categorical data. Correlation analyses were performed using the Pearson correlation test in case of normally distributed variables and Spearmen correlation test for non-normally distributed variables. Analysis of variance (ANOVA) used to compare the means of more than two samples and Tukey's honestly significant difference (HSD) test was used for post-hoc analysis. The simple size was calculated at 95% confidence interval by using G-Power-3.1.9.2. Program. Because of the posthoc analysis, the standardized effect size at α =0.005 level was calculated as 0.78.

RESULTS

A total of 122 patients enrolled in this study (n=62 patients in FMF group, n=60 patients in control group). Demographic and laboratory findings of the study represented in Table 1. There was no significant difference between the two groups in terms of age and sex. When the groups compared in terms of MHR, the difference between the two groups was insignificant (p=0.836).

According to mutation types,FMF group divided into 4 subgroups: heterozygous mutations (n=24), compound mutations (n=11), homozygous mutations (n=4), negative (n=21), and 2 were not analyzed. All the mutation types given in Table 2. The MHR was higher in negative mutation type than others were but this difference is not significant. There was no significant difference between these four groups according to MHR (p=0.348).

In correlation analysis, MHR revealed a positive correlation with SAA (r=0.437, p=0.005, n=39), fibrinogen (r=0.604, p<0.005, n=24), CRP (r=0.277, p=0.005, n=101), and ESR (r=0.404, p<0.001, n=104) (Figure 1, 2, 3 and 4, respectively).

Table 1. Comparison of demographic characteristics and laboratory parameters of groups

Parameters	FMF Group (n=62)	Control Group (n=60)	p
Age,year, median (IQR)	10 (7-12)	11 (6-15)	0.613
Female (n, %)	28 (45.2)	28 (46.7)	0.868
WBC, x10^3/mm^3, median (IQR)	7.10 (6.00-85.00)	7.80 (6.60-9.00)	0.089
Hb, g/dl, mean± SD	13.02±0.87	12.97±1.05	0.764
Platelet count x10^3/mm^3,mean±SD	287.49±536.42	299.38±707.59	0.300
MPV, median (IQR)	8.00 (7.10-9.95)	7.80 (7.30-8.70)	0.779
RDW, mean±SD	42.21±4.49	42.52±4.18	0.696
Monocyte countx10^3/mm^3, median (IQR)	0.50 (0.40-0.60)	0.50 (0.40-0.70)	0.881
HDL, mg/dl, mean±SD	52.52±12.72	50.82±12.65	0.491
MHR, median (IQR)	9.80 (7.57-14.28)	10.25 (7.40-14.00)	0.836
CRP, mg/dl, median (IQR)	0.08 (0.04-0.36)	0.12 (0.05-0.32)	0.855
ESR, mm/h, median (IQR)	7.00 (5.00-17.00)	8.00 (5.00-13.00)	0.875
NLR, mean±SD	2.64±3.67	2.56±2.97	0.896
PLR, mean±SD	169.28±179.63	151.26±106.78	0.507

IQR: Interquartile range, WBC: White blood cell, Hb: Hemoglobin, MPV: Mean platelet volume, RDW: Red cell distribution width, HDL: High density lipoprotein, MHR: Monocyte HDL ratio, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, NLR: Neutrophil lymphocyte ratio, PLR: Platelet lymphocyte ratio. Data are presented as mean ± standard deviation (SD) number, median (interquartile range) and percentage, p ≤ 0.05 was considered statistically significant

Table 2. Mutation analysis of FMF group

Mutation Group	Mutation Types	(n) %
Homozygous	M694V, P369S,	(4) 6.45
Compound	HetM694V/HetR202Q, HetE148Q/ HetM680I, Hetp369S/HetPR408Q/ Hom202Q, HetM694V/HetV726A, HomM694V/HomR202Q, HetM694V/ HetE148Q, HetE148Q/HetPL110P	(11) 17.74
Negative, other		(21) 33.87
Not analyzed		(2) 3.22

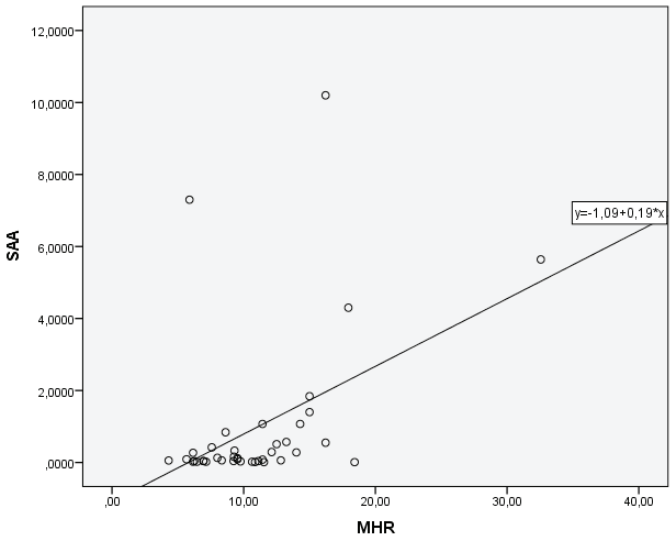

Figure 1. Correlation between MHR and SAA

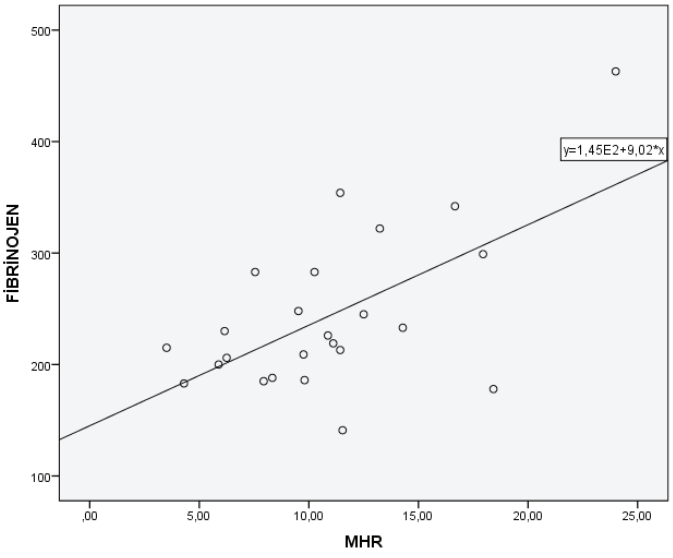

Figure 2. Correlation between MHR and fibrinogen

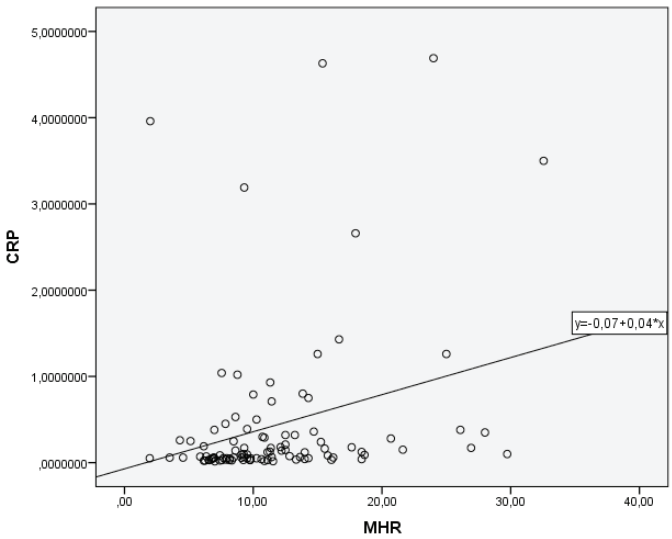

Figure 3. Correlation between MHR and CRP

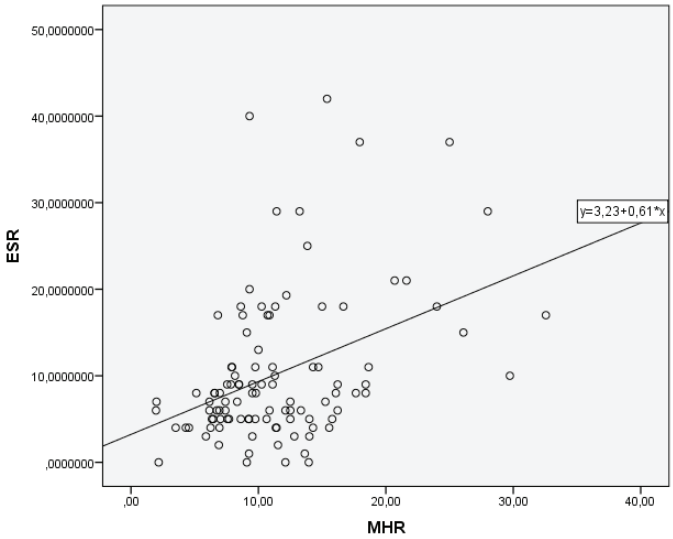

Figure 4. Correlation between MHR and Erythrocyte Sedimentation Ratio

DISCUSSION

In the present study, we evaluated the relationship between MHR-which is a newly introduced inflammatory marker-and FMF in children. We have seen that there is no study-related this issue when we scan the literature. Clinical and laboratory variables evaluated in FMF patients and compared them to the healthy control group. Our findings showed that MHR is similar in both groups and there is no statistical difference between them. We also compare the other parameters that thought to be the indicator of inflammation such as MPV, PLR, NLR, RDW and no significant difference was found between the groups, too.

It claimed that there was a vascular endothelial dysfunction in FMF and chronic inflammation causes this condition (22). Normal endothelial cells have anti-inflammatory

properties and endothelial functions reduce in presence of inflammatory conditions. This causes oxidative stress and it results in endothelial dysfunction (23). Güneş et al. (22) found endothelial dysfunction in FMF patients and its relationship with microalbuminuria. Subclinical inflammation continues even in attack-free periods and this inflammation causes atherosclerosis and vascular damage (24,25).

The activation of monocytes plays an important role in immune defenses in chronic inflammatory conditions and this can be related to inflammatory cytokines (26). Tumor necrosis factor, monocytes, and macrophages may damage the endothelium. It has been suggested that HDL-C has anti-inflammatory and protective roles in vascular endothelial cells (12). It inhibits circulating inflammatory cells, leukocyte and platelet activation (27). High monocyte count and low HDL-C levels can be indirect indicators of inflammation in atherosclerosis process (26). From this point, it can be suggested that the ratios of these two values are related to inflammation. There are many studies in the literature related to MHR and its relationship with inflammation. Kanbay et al. (14) showed that increased MHR affects the cardiovascular prognosis poorly in their study of chronic kidney disease. Vahit et al. (20) demonstrated MHR could be used as an indicator of metabolic syndromes. Çetin et al. (16) showed that MHR in acute coronary syndrome could be used as an effective marker of inflammation on the severity of future cardiovascular events and coronary artery disease. Usta et al. (28) stated that MHR can used as a marker of detection of cardiovascular risk on polycystic ovary syndrome. Another study on erectile dysfunction (ED) has shown that MHR is elevated in patients with ED, and this may be associated with inflammation (29). It has been suggested that MHR has a relationship with systemic inflammation and endothelial dysfunction. Açıkgöz et al. (30) found a strong inverse correlation between MHR and flow-mediated dilatation that is a method to show endothelial dysfunction- in Behçet's disease.

Contrary to these studies, we found in our study, there was no difference between healthy controls and FMF patients in terms of MHR. We have also examined the PLR, MPV, RDW and NLR values which have been previously suggested to be used as markers of inflammation in FMF in most studies (5,31,32), but we have found that these values are statistically insignificant in both groups. This condition may be because all patients were in attack-free period, or as mentioned, it weakens the argument that MHR can be used as a marker of inflammation. Since inflammation will not occur in FMF patients during attack-free periods, there may be decreases in inflammatory response indicators.Inflammation in FMF is limited after a certain period of time. Due to this condition, HDL-C, which is a marker of ongoing chronic inflammatory events, may not be suitable for FMF.However, we found a positive correlation between MHR and other inflammatory markers such as CRP, ESR, fibrinogen, and SAA that used in FMF. It shows association with systemic inflammation. Canpolat et al. (15) demonstrated a positive correlation between hs-CRP and MHR, which supports its role in systemic inflammation.

The gene (MEFV) responsible for FMF is located on the short arm of chromosome 16. To date, more than 40 mutations have been associated with the disease. A single mutation detected in 25% of the patients with FMF (carrier), or none of the known mutations can be shown. Four of the five most frequent mutations are in exon 10 (M694V, V726A, M694I, M680I) and one in exon 2 (E148Q) (33). Some studies showed a correlation between amyloidosis and the mutation M694V (34). In another study conducted by Kıncır et al. (35) of 700 children with FMF, demonstrated an acute phase reactant response was highest in M694V and E148Q. In our study, 40.32% of the patients had M694V mutation that is consistent with the literature. When we classified the patients according to their genes, we observed that the MHR did not differ between the groups and within the groups.

Our study should be interpreted with some limitations. First, because of its retrospective design, patients were not classified as attack or attack-free.Our study can be strengthened with comparing the patients in attack period but we cannot reach the data of the patients in attack period because they did not apply to outpatient clinics in that time. Due to deficiencies in the emergency department records, the records of the patients could not be reached.This has once again demonstrated that emergency department records must be kept strictly both legally and scientifically.Second, extra examinations could be performed to prove endothelial dysfunction, but this was not possible because of its retrospective design, too. Third, we have no data about complications of FMF to examine the relationship with MHR.

CONCLUSION

In conclusion, our findings revealed that no significant difference between the groups in terms of MHR. In addition, MHR was positively correlated with other inflammatory markers such as CRP, ESR, SAA, and fibrinogen. These results suggested thatthe use of MHR as a marker of inflammation in FMF might be suspicious.

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REFERENCES

1. Tunca M, Akar S, Onen F, et al. Turkish FMF Study Group. Familial Mediterranean fever (FMF) in Turkey: results of a nationwide multicenter study. Med (Baltimore) 2005;84:1-11.

2. Sarı I, Birlik M, Kasifoglu T. Familial Mediterra¬nean fever: an updated review. Eur J Rheum 2014;1:21-3.
3. Ben-Zvi I, Livneh A. Chronic inflammation in FMF: markers, risk factors, out¬comes and therapy. Nat Rev Rheumatol 2011;7:105-12.
4. Zahorec R. Ratio of neutrophil to lymphocyte counts-rapid and simple parameter of systemic inflammation and stress in critically ill. Bratisl Lek Listy 2001;102:5-14.
5. Ahsen A, Ulu MS, Yuksel S, et al. As a new inflammatory marker for familial Mediterranean fever: neutrophil-to-lymphocyte ratio. Inflammation 2013;36:1357-62.
6. Sakalli H, Kal O. Mean platelet volume as a potential predictor of protein¬uria and amyloidosis in familial Mediterranean fever. Clin Rheumatol 2013;l 32:1185-90.
7. Hu ZD, Chen Y, Zhang L, et al. Red blood cell distribution width is a poten¬tial index to assess the disease activity of systemic lupus erythematosus. Clin Chim Acta 2013;425:202-5.
8. Akbas EM, Demirtas L, Ozcicek A, et al. Association of epicardial adipose tis¬sue, neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio with diabetic nephropathy. Int J Clin Exp Med 2014;7:1794-801.
9. Ancuta P, Wang J, Gabuzda D. CD16+ monocytes produce IL-6, CCL2, and matrix metalloproteinase-9 upon interaction with CX3CL1-expressing endothelial cells. J Leukoc Biol 2006;80:1156-64.
10. Auffray C, Sieweke MH, Geissmann F. Blood monocytes: development, heterogeneity, and relationship with dendritic cells. Annu Rev Immunol 2009;27:669-92.
11. Linker R, Gold R, Luhder F. Function of neurotrophic factors beyond the nervous system: inflammation and autoimmune demyelination. Crit Rev Immunol 2009;29:43-68.
12. Parthasarathy S, Barnett J, Fong LG. High-density lipoprotein inhibits the oxidative modification of low-density lipoprotein. Biochim Biophys Acta 1990;1044:275-83.
13. Westerterp M, Gourion-Arsiquaud S, Murphy AJ, Shih A, Cremers S, Levine RL,et al. Regulation of hematopoietic stem and progenitor cell mobilization by cholesterol efflux pathways. Cell Stem Cell 2012;11:195-206.
14. Kanbay M, Solak Y, Unal HU, et al. Monocyte count/HDL cholesterol ratio and cardiovascular events in patients with chronic kidney disease. Int Urol Nephrol 2014;46:1619-25.
15. Canpolat U, Çetin EH, Cetin S, et al. Association of Monocyte-to-HDL cholesterol ratio with slow coronary flow is linked to systemic inflammation. Clin Appl Thromb 2016;22:476-82.
16. Cetin MS, Ozcan Cetin EH, Kalender E, et al. Monocyte to HDL cholesterol ratio predicts coronary artery disease severity and future major cardiovascular adverse events in acute coronary syndrome. Heart Lung Circ 2016;25:1077-86.
17. Cagli K, Tok D, Turak O, et al. Monocyte count to-high-density lipoprotein-cholesterol ratio is associated with abdominal aortic aneurysm size. Biomark Med 2016;10:1039-47.
18. You S, Zhong C, Zheng D, et al. Monocyte to HDL cholesterol ratio is associated with discharge and 3-month outcome in patients with acute intracerebral hemorrhage. J Neurol Sci 2017;372:157-61.
19. Aydin E, Ates I, Fettah Arikan, et al. The ratio of monocyte frequency to HDL cholesterol level as a predictor of asymptomatic organ damage in patients with primary hypertension. Hypertens Res 2017;40:758-64.
20. Vahit D, Mehmet KA, Samet Y, et al. Assessment of monocyte to high density lipoprotein cholesterol ratio and lymphocyte-to-monocyte ratio in patients with metabolic syndrome. Biomark Med 2017;11:535-40.
21. Livneh A, Langevitz P, Zemer D, et al. Criteria for the diagnosis of familial Mediterranean fever. Arthritis Rheum 1997;40:1879-85.
22. Güneş H, Kıvrak T, Tatlısu M, Kaya H, Yılmaz MB. Relationship between endothelial dysfunction and microalbuminuria in familial Mediterranean fever. Eur J Rheumatol 2016;3:61-64.
23. Vlachopoulos C, Rokkas K, Ioakeimidis N, et al. Inflammation, metabolic syndrome, erectile dysfunction, and coronary artery disease: common links. Eur Urol 2007;52:1590-600.
24. Drenth JP, van der Meer JW. Hereditary periodic fever. N Engl J Med 2001;345:1748-57.
25. Holmes AH, Booth DR, Hawkins PN. Familial Mediterranean fever gene. N Engl J Med 1998; 338:992-3.
26. Akboga MK, Balci KG, Ertem AG, et al. Usefulness of monocyte to HDL-cholesterol ratio to predict high SYNTAX score in patients with stable coronary artery disease. Biomark Med 2016; 10:375-83.
27. Açıkgöz SK, Açıkgöz E, Şensoy B, et al. Monocyte to high-density lipoprotein cholesterol ratio is predictive of in-hospital and five-year mortality in ST-segment elevation myocardial infarction. Cardiol J 2016;23:505-12.
28. Usta A, Avci E, Bulbul CB, et al. The monocyte counts to HDL cholesterol ratio in obese and lean patients with polycystic ovary syndrome. Reprod Biol Endocrinol 2018;16:34.
29. Kadihasanoglu M, Karabay E, Yucetas U, et al. Relation between Monocyte to High-Density Lipoprotein Cholesterol Ratio and Presence and Severity of Erectile Dysfunction. Aktuelle Urol 2018;49:256-61.
30. Acikgoz N, Kurtoglu E, Yagmur J, et al. Elevated monocyte to high-density lipoprotein cholesterol ratio and endothelial dysfunction in Behçet disease. Angiology 2018;69:65-70.
31. Özer S, Yılmaz R, Sönmezgöz E, et al. Simplemarkers for subclinical inflammation in patients with Familial Mediterranean Fever. Med Sci Monit 2015;21:298-303.
32. Gasparyan AY, Sandoo A, Stavropoulos-Kalinoglou A, et al. Mean plate¬let volume in patients with rheumatoid arthritis: the effect of anti-TNF-al¬pha therapy. Rheumatol Int 2010;30:1125-9.
33. Kasapçopur Ö, Arısoy N. Familial Mediterranean Fever and other hereditary auto inflammatory diseases. Turk Pediatri Ars 2010;41:9- 17.
34. Shohat M, Magal N, Shohat T, et al. Phenotype-genotype correlation in familial Mediterranean fever: evidence for an association between Met694Val and amyloidosis. Eur JHum Genet 1999;7:287-92.
35. Kıncır M, Duksal F, Cevit O, et al. Association of clinical and genetic features in familial mediterranean fever among children from central anatolia, Turkey. Proc. Natl. Acad. Sci., India, Sect B Biol Sci 2015;85:793-800.