Received: 31 Jan 2023 | **Accepted:** 20 Feb 2023 **Genel Tıp Derg. Volume** 33/**Issue** 1 (February), 100-105
DOI: 10.54005/geneltip.1245252

ORIGINAL ARTICLE

Comparison of Monocyte/Hdl-C Ratıos in Sub-Groups of Ischemıc Stroke According to Etiology

İskemik İnmenin Etyolojiye Göre Alt Gruplarında Monosit/Hdl-K Oranlarının Karşılaştırılması

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How to cite ?

Gündüz Z. B. Comparison of Monocyte/Hdl-C Ratıos in Sub-Groups of Ischemıc Stroke According to Etiology. Genel Tıp Dergisi. 2023; 33(1): 100-105.

ABSTRACT

Background/Aim: The increase in (MHR) values calculated by the ratio of monocyte to high-density lipoprotein cholesterol (HDL-C) is a parameter that has recently been evaluated as a measure of inflammation and oxidative stress.There are data associated with cardiovascular diseases and carotid artery pathologies.The aim of this study is to seek an answer to the question "Can MHR be a guiding parameter in the differentiation of these pathologies that are blamed in the etiology of ischemic stroke?"
Methods: The records of 200 patients with the diagnosis of acute ischemic stroke and whose neurological examination, neuroradiological imaging and monocyte and HDL-C examinations were completed within the first 24 hours after the onset of symptoms were evaluated retrospectively. They were grouped according to the TOAST classification.Measured monocyte values, HDL-C values and MHR values obtained by monocyte/HDL-C ratio were analyzed statistically according to TOAST groups, comorbid diseases and gender.
Results: There was a statistically significant increase in MHR in male and in diabetics, without any statistically significant difference between TOAST groups in terms of MHR.
Conclusion:MHR is not an appropriate parameter to use in the estimation of these groups, as it does not show any difference between the subgroups of stroke depending on the etiology.

Keywords: monocytes/HDL-C, MHR, ischemic stroke, TOAST classification

ÖZ

Amaç: Monositin yüksek yoğunluklu lipoprotein kolesterole (HDL-K) oranlanmasıyla hesaplanan MHR değerlerinin artışı, son zamanlarda inflamasyon ve oksidatif stres ölçütü olarak değerlendirilen bir parametredir. Kardiyovasküler hastalıklarla ve karotis arter patolojileriyle ilişkilendirildiği veriler mevcuttur. Bu çalışmanın amacı 'MHR iskemik inmenin etyolojisinde suçlanan bu patolojilerin ayrımında yönlendirici olabilecek bir parametre olabilir mi?' sorusuna cevap aramaktır.
Yöntem: Akut iskemik inme tanısıyla tedavi edilen 200 hastanın kaydı retrospektif olarak incelendi. Hastalardan semptomlarının ilk 24 saati içinde nörolojik muayenesi, nöroradyolojik görüntülemesi (difüzyon mrg ve/veya BBT ile) ve monosit ve HDL-K tetkikleri tamamlanmış, yatışı süresince etyolojiye yönelik tetkikleri sonuçlanan, dışlama kriterleri göz önünde tutularak seçilenler, TOAST sınıflamasına göre gruplandırıldı. Ölçülen monosit değerleri, HDL-K değerleri ve monosit/HDL-K oranlanmasıyla elde edilen MHR değerleri TOAST gruplarına, eşlik eden hastalıklara ve cinsiyete göre istatistiksel olarak incelendi.
Bulgular: MHR açısından TOAST grupları arasında istatistiksel olarak anlamlı farklılık gözlenmeksizin erkeklerde ve diyabetik olanlarda MHR değerinde istatistiksel olarak anlamlı yükseklik mevcuttu.
Sonuç: MHR, inmenin etyolojiye bağlı alt grupları arasında herhangi bir farklılık göstermediği için bu grupların tahmininde kullanılması uygun bir parametre değildir

Anahtar kelimeler: monosit/HDL-K, MHR, iskemik inme, TOAST sınıflaması

Introduction

Ischemic stroke is a leading cause of death and disability worldwide. Inflammatory mechanisms are thought to play a critical role in the pathological processes of ischemic stroke and its subtypes. There are publications showing an independent relationship between total white blood cell count and stroke risk, stroke severity and mortality (1–4).

Monocytes/macrophages and T-lymphocytes are responsible for the production, infiltration and lipid core formation of inflammatory cytokines, which are thought to be involved in the pathogenesis of stroke, and are held responsible for the aggravation of brain damage and atherosclerotic plaque formation through this mechanism (5-7). Conversely, high-density lipoprotein cholesterol (HDL-C) exerts anti-inflammatory, antioxidant, and antithrombotic effects by reversing cholesterol transport and preventing endothelial dysfunction (8). Therefore, it is thought that the monocyte-to-high-density lipoprotein cholesterol ratio (MHR) may be a systematic inflammatory marker associated with atherosclerosis (9).

In terms of the pathogenesis of atherosclerosis, HDL-C level is a lipid parameter that decreases in the presence of endothelial dysfunction and atherosclerosis, while monocytes are a hematological index that increases during inflammation. In this regard, theoretically, in atherosclerosis cases, while HDL-C levels decrease, monocyte levels increase, so the MHR value is expected to increase (10). Publications suggesting that an increase in MHR indicates an increased risk of carotid plaque

Peer-Review: Double anonymized - Two External
Plagiarism Checks: Yes - Turnitin
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formation and can be used as a possible marker for plaque formation and severity may be relevant in this regard (11).

On the other hand, data linking MHR with cardiac disease through the same inflammatory procedures is also abundant. Preoperative MHR elevation may be an important biomarker to predict early recurrence after atrial fibrillation ablation (12). Increased MHR may predict the risk of developing intra-stent restenosis after coronary angiography, and may be associated with higher long-term mortality and long-term major cardiac adverse events in patients with coronary heart disease (13,14).

Data based on ischemic stroke patients suggest that high MHR level is associated with high mortality but low risk of hemorrhagic transformation (15,16).

Although data on the relationship of MHR with cardiac and cerebrovascular events are mostly shared on predicting survival and prognosis, data on the role of inflammation in the etiology are quite limited.

Ischemic stroke classification is critical in the conduct of basic research and clinical practice. Analysis of stroke subtypes requires the integration of clinical features, findings from diagnostic tests, and data on potential etiologic factors derived from clinician assessment. Two main approaches to etiological classifications of ischemic stroke are used: causal and phenotypic subtyping. The most widely used cause-based system is the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification. Although new classifications developed over time have been introduced, they are not as accepted as the TOAST classification (17,18).

The TOAST classification is an ischemic stroke subtype categorization system based on etiology developed for the Trial of Org 10172 in Acute Stroke Treatment and evaluated in 5 categories: 1-large-artery atherosclerosis, 2- cardioembolism, 3-small-vessel occlusion, 4- stroke of other determined etiology, 5- stroke of undetermined etiology. (18).

In this study, it was aimed to examine the MHR values of the subgroups according to the TOAST classification in acute ischemic stroke patients and to reveal the data on whether this parameter can be effective in the evaluation of the etiology.

Material Methods

The study protocol was approved by the Selcuk University Medical Faculty Ethics Committee (2023/02-2023/60). The hospital records of 200 patients who were admitted to the Konya City Hospital Department of Neurology with the diagnosis of acute ischemic stroke and whose neurological examination, neuroradiological imaging (with diffusion MRI and/or CT) and monocyte and HDL-C examinations were completed within the first 24 hours after the onset of symptoms were evaluated retrospectively. They were grouped according to the TOAST classification.

In the TOAST classification, patients are evaluated in 5 categories: 1-Large-artery atherosclerosis, 2-Cardioembolism, 3-Small-vessel occlusion, 4- Stroke of other determined etiology, 5- Stroke of undetermined etiology.

The following criteria were considered for patient grouping;

1st Group; Large artery atherosclerosis: Patients with clinical or imaging evidence of severe (>50%) stenosis or occlusion of neck or brain vessels due to atherosclerosis, loss of cerebral cortical function (aphasia, motor impairment, etc.) or clinical signs of brain stem or cerebellar dysfunction,

2nd Group; Cardioembolic patients: patients in whom at least one source of cardiac embolism has been identified,

3rd Group; small-vessel occlusion: Patient group with one of the clinical lacunar syndromes and without cerebral cortical dysfunction. A history of diabetes mellitus or hypertension supports the diagnosis. The patient should also have a normal CT/MRI scan or a brain stem or subcortical hemispheric lesion less than 1.5 cm in diameter.

4th Group; Stroke of other determined etiology: Patients with rare causes of stroke such as non-atherosclerotic vasculopathy, hypercoagulability or hematological disorders,

5th Group; Stroke of undetermined etiology: Patients in whom the cause of the stroke cannot be reliably established, an etiology cannot be established despite extensive investigation, or there is more than one potential cause, and the physician cannot clarify the exact cause (18).

Patients with rheumatological and/or oncological diseases whose treatment has not been completed, those with liver and kidney failure that require treatment, those with a history of acute coronary syndrome, cardiac surgery, ischemic/hemorrhagic stroke or endovascular treatment within 3 months before the date of application, those who had acute infection findings at the time of admission to the hospital, and whose neurological status was evaluated as transient ischemic attack, no signs of acute ischemia observed in central imaging, patients who underwent intravenous thrombolytic therapy and/or endovascular therapy (thrombectomy and/or stent) before monocyte and HDL-C tests were completed, and whose hospitalization ended in death or discharge before the completion of carotid imaging and cardiac examinations for etiology were not included in the study.

The measured monocyte values, HDL-C values and MHR values obtained by the ratio of these monocyte/HDL-C were analyzed statistically according to TOAST groups, comorbidities and gender.

Statistical Analysis

IBM SPSS Statistics 21. Software program was used for statistical analysis. Frequency and percentage values were used as descriptive statistics for nominal categorical data. For numerical variables, firstly, to evaluate the normality of their distribution: skewness and kurtosis values and their z-scores, Pearson skewness coefficient and Kolmogorov-Smirnov test (if number of samples ≥ 30) or Shapiro-Wilk test (if number of samples < 30) were used.

Since the distribution of our numerical variables was not normal, minimum and maximum values were given along with the median value. The χ2 test was used to compare nominal categorical data. While the Mann-Whitney U test was used to compare the numerical variables of the two groups, the Kruskal Wallis test was used to compare the numerical variables of more than two groups. If statistical difference was detected in Kruskal Wallis test, Mann Whitney U test was used with Bonferroni correction in pairwise comparisons of groups. If the alpha value (p) was less than 0.05, it was considered statistically significant.

Results

Two hundred patients were evaluated according to the TOAST classification; 21 large artery atherosclerosis (group 1), 65 cardioembolic origin (group 2), 42 small vessel occlusion (group 3), 2 other specified causes (group 4), and 70 stroke with undetermined cause (group 5). Group 4 could not be included in the statistical evaluation due to the small number of patients.

MHR median values were 0.0153 (0.005-0.025) in the 1st group, 0.1459 (0.0036-0.0380) in the 2nd group, 0.1233 (0.0011-0.0329) in the 3rd group, and in the 5th group It was calculated as 0.0159(0.0016-0.0435). No statistically significant difference was observed between the TOAST groups in terms of MHR. Monocyte counts were the lowest in Group 5, but the difference was statistically significant only with Group 3 (p=0.03) (Table 1).

The parameters in which MHR was significantly affected were the presence of diabetes mellitus and gender. It was higher in men than in women (p<0.0001) and in diabetics compared to nondiabetics (p=0.025).

Table 1 TOAST Group and patient characteristics

	TOAST			
	1	**2**	**3**	**5**
Sex				
Male	18 (15.4%)	28 (23.9%)	26 (22.2%)	45 (38.5%)
Female	3 (3.7%)	37 (45.7%)	16 (19.8%)	25 (30.9%)
$X^2(3) = 13.972$, p = 0.03, Cramer's V = 0.003				
Age years, median (min-max)	70 (54-84)	73 (40-89)	65.5 (45-88)	70 (39-93)
Kruskal Wallis test, $X^2(3) = 0.081$				
Stroke count, median (min-max)	1 (1-3)	1 (1-3)	1 (1-5)	1 (1-3)
Kruskal Wallis test, $X^2(3) = 5.203$, p = 0.153				
Stroke localization				
Anterior	16 (14%)	38 (33.3%)	11 (9.6)	49 (43%)
Posterior	4 (5.5%)	20 (27.4%)	30 (41.1%)	19 (26%)
Multiple	1 (9.1%)	7 (63.6%)	1 (9.1%)	2 (18.2)
The analysis could not be performed because it did not provide the necessary assumptions for the Chi-square test.				
mRS score, median (min-max)	3 (1-4)	3 (1-5)	2.5 (1-5)	3 (1-5)
Kruskal Wallis test, $X^2(3) = 4.365$, p = 0.225				
Hospital stay, median (min-max)	5 (1-16)	7 (2-37)	6 (2-12)	5 (2-28)
Kruskal Wallis testi, $X^2(3) = 8.587$, p = 0.035; Statistically significant difference between TOAST 2 and 3 after Bonferroni test p = 0.036				
Number of monocytes	0.55 (0.18-0.88)	0.62 (0.18-1.75)	0.515 (0.05-1.34)	0.66 (0.09-1.11)
Kruskal Wallis test, $X^2(3) = 10.462$, p = 0.015; The difference between TOAST 3 and 5 after Bonferroni test was statistically significant p = 0.03				
HDL level	37 (24-63)	43 (24-72)	44 (26-86)	44 (23-72)
Kruskal Wallis test, $X^2(3) = 6.5$, p = 0.090				
MHR ratio	0.0153 (0.005-0.025)	0.1459 (0.0036 -0.0380)	0.1233 (0.0011-0.0329)	0.0159 (0.0016-0.0435)
Kruskal Wallis test, $X^2(3) = 5.513$, p = 0.138				

TOAST;Trial of Org 10172 in Acute Stroke Treatment group1;large-artery atherosclerosis, 2; cardioembolism, 3;small-vessel occlusion,, 5; stroke of undetermined etiology. HDL; high-density lipoprotein MHR; ratio of monocyte to high-density lipoprotein cholesterol mRS modified Rankin Scale

Table 2 MHR evaluation according to the presence of other diseases and clinical features

	Monocyte count	HDL level	MHR
Sex			
Male	0.61 (0.05-1.33)	39 (23-71)	0.0165 (0.0011-0.0435)
Female	0.59 (0.09-1.75)	47 (24-86)	0.0125 (0.0016-0.0321)
Mann Whitney U test	4393.5	2495.0	3295.5
p- values	0.384	<0.0001	<0.0001
Stroke localization			
Anterior	0.625 (0.09-1.75)	43 (23-86)	0.0146 (0.0016-0.0435)
Posterior	0.57 (0.05-1.34)	41 (24-62)	0.0140 (0.0011-0.0329)
Multiple	0.62 (0.45-0.9)	49 (32-66)	0.0122 (0.009-0.0265)
Kruskal Wallis test	$X^2(2) = 3.4$, p = 0.183	$X^2(2) = 6.108$, p = 0.047 Anterior & Posterior p = 0.032	X^2 (2) = 0.492, p = 0.782
Hypertension			
No	0.72 (0.16-1.080)	44 (27-68)	0.0154 (0.0027-0.0319)
Yes	0.59 (0.05-1.75)	42,5 (23-86)	0.0139 (0.0011-0.0435)
Mann Whitney U test	1696.5	2035	2076.5
p-values	0.015	0.219	0.280
Diabetes mellitus			
No	0.61 (0.05-1.33)	44 (23-86)	0.0132 (0.0011-0.0435)
Yes	0.6 (0.09-1.75)	37 (24-66)	0.0159 (0.0016-0.0329)
Mann Whitney U test	4496.5	3302	3735
P values	0.767	0.001	0.025
Heart Failure			
No	0.61 (0.09-1.75)	43 (23-86)	0.0138 (0.0016-0.0435)
Yes	0.61 (0.05-1.09)	43 (24-68)	0.0158 (0.0011-0.0297)
Mann Whitney U test	2452	2701	2535
p-values	0.368	0.943	0.533
Coronary heart disease			
No	0.605 (0.05-1.750)	43 (23-86)	0.0138 (0.0011-0.0435)
Yes	0.61 (0.09-1.09)	41 (24-66)	0.0157 (0.0016-0.0293)
Mann Whitney U test	3256	3121.5	3108.5
p-values	0.952	0.639	0.611
Atrial fibrillation			
No	0.61 (0.05-1.75)	43 (23-86)	0.0138 (0.0011-0.0435)
Yes	0.62 (0.25-1.33)	41 (24-72)	0.015 (0.0047-0.0380)
Mann Whitney U test	3817.5	4085.5	4038.5
p-values	0.443	0.968	0.866
Hyperlipidemia			
No	0.61 (0.05-1.75)	43 (23-86)	0.0146 (0.0011-0.0435)
Yes	0.59 (0.09-1.34)	43 (24-72)	0.0130 (0.0016-0.0329)
Mann Whitney U test	4275.5	4291	4193.5
P-values	0.389	0.411	0.284
Demantia			
No	0.61 (0.05-1.75)	43 (23-86)	0.143 (0.0011-0.0435)
Yes	0.55 (0.32-1.11)	42,5 (34-62)	0.0121 (0.0058-0.0326)
Mann Whitney U test	1330	1417.5	1260
P-values	0.211	0.382	0.12
Parkinson disease			
No	0.61 (0.05-1.75)	43 (23-86)	0.0142 (0.0011-0.0435)
Yes	0.61 (036-1.0)	43 (38-47)	0.0135 (0.084-0.0218)
Mann Whitney U test	482.5	482	472
p-values	0.999	0.997	0.934
Epilepsy			
No	0.61 (0.05-1.75)	43 (23-86)	0.0142 (0.0011-0.0435)
Yes	0.59 (0.46-0.71)	39.5 (24-58)	0.015 (0.0079-0.0296)
Mann Whitney U test	343.5	330	366
p-values	0.695	0.609	0.846
Anticoagulant using			
No	0.59 (0.05-1.75)	43 (23-86)	0.0139 (0.0011-0.0435)
Yes	0.68 (0.26-1.11)	43 (28-72)	0.0158 (0.0047-0.0326)
Mann Whitney U test	1690.5	2160	1930
p-values	0.045	0.78	0.261
antiagregant using			
No	0.61 (0.16-1.75)	43 (23-86)	0.0142 (0.0027-0.0435)
Yes	0.6 (0.05-1.11)	40 (24-68)	0.0145 (0.0011-0.0329)
Mann-Whitney U test	3517.5	3286	3603.5
p-values	0.622	0.237	0.783

MHR; ratio of monocyte to high-density lipoprotein cholesterol , HDL; high-density lipoprotein

HDL was also significantly higher in females (p<0.0001) and non-diabetic subjects (p=0.001). Presence of hypertension was associated with low monocyte count (p=0.015), but no effect on MHR was observed. HDL-C level was significantly lower in the group with posterior circulation ischemia compared to the group with anterior circulation ischemia (p= 0.047).

There was no difference between the groups in terms of heart failure, coronary heart disease, atrial fibrillation and hyperlipidemia, and monocytes, HDL-C and MHR. History of dementia, Parkinson's disease and presence of epilepsy were also ineffective for all three parameters. There was no correlation between the use of antiaggregants before stroke and monocytes, HDL-C and MHR. However, the median monocyte value was significantly higher in those using anticoagulants before stroke (p=0.045), and no correlation was found with HDL-C and MHR (Table 2).

No difference was observed between the TOAST groups in terms of age, number of strokes, and modified Rankin score (MRS), but when the gender ratio for the groups was, it was determined that it significantly increased in favor of female gender only in the cardioembolic group (p=0.03). The hospital stay was longer in the cardioembolic group than in all groups, but this difference was statistically significant only in Group 3 (p=0.036).

Discussion

The search for biomarkers that can save time in diagnosis or help predict prognosis continues to be the subject of studies. This issue is of particular importance in cases that require urgent diagnosis and treatment, such as acute cardiovascular diseases and acute cerebrovascular diseases.

MHR obtained by dividing the monocyte value by HDL-C; It is a biomarker that has been the subject of many publications where it is found significant in terms of inflammation, and the fact that it is a parameter calculated using easily accessible routine blood tests in many patient groups has played an important role in the spread of studies.

A meta-analysis study evaluating the relationship of MHR to survival in cardiac diseases in large patient groups shows that increased MHR is associated with higher long-term mortality and increased major cardiac adverse events in coronary heart disease. It indicates that MHR may serve as a potential prognostic indicator for risk stratification in this patient group (14). In another study, it was reported that the MHR value was higher in stroke patients than the control group without specifying the subgroup, and that higher MHR was a significant parameter in predicting 30-day mortality (15). A different study on MHR in ischemic stroke associates high MHR with poor prognosis in the presence of large artery atherosclerosis (19). Large patient population-based data have been published showing that MHR levels increase as carotid plaque severity increases in those without hypertension or diabetes (11). Data related to MHR in stroke have been interpreted mostly on prognosis. In a study in which 477 patients were evaluated retrospectively, the clinically and radiologically revealed progressive stroke clinic in 147 patients was associated with increased MHR, especially in the group with large artery disease (20).

Contrary to the pathologies associated with the carotid, we did not find any study in the literature on stroke patients associated with cardiac etiology. The reason for this is that medium and high risk cardiac diseases that play a role in the etiology of ischemic stroke have a wide spectrum ranging from cardiac rhythm disorders to developmental cardiac anomalies, acquired heart valve diseases, congestive heart failure, infective endocarditis and coronary syndromes. Therefore, all these diseases that develop with different mechanisms may not have the same effect on MHR.

In our study, when TOAST groups were compared, no significant difference could be found in MHR values between groups based on different etiologies. While examining the reasons for this, we think that it should be taken into consideration that this inflammation marker is associated with many diseases and factors in previous studies, the presence of which was also reported in our patient groups. In a study examining the relationship between MHR and carotid intima-media thickness (CIMT) in patients with type 2 diabetes, it was stated that high MHR was in a significant relationship with CIMT only in the presence of male gender (21). Our data also reveal that the MHR value is significantly higher in male gender regardless of the group.

It has also been reported that MHR may be an important long-term marker in predicting individuals who will develop diabetes in the community, and this relationship is also affected by hypertension, presence of excess weight or smoking habits (22). In our patient group, HDL was significantly lower in the diabetic patient group compared to nondiabetics, which was reflected in a statistically significant increase in the MHR parameter. Data were also shared, showing that there was a continuous positive linear relationship between MHR and hypertension (23). Although a negative relationship was observed between the presence of hypertension and only monocyte values in our patient group, no significant reflection of this relationship on MHR was observed. On the other hand, these factors were excluded from our study, since the registration information on body/mass index and smoking habits could not be accessed retrospectively in all patients.

Another limiting factor was that a large number of patients excluded from our study, as MHR was affected by so many factors. In our study, the stroke group due to large vessel atherosclerosis, which was mostly associated with MHR in the literature, was in the minority, especially in patients with large vessel lesions that developed more rapidly and presented with

severe clinical findings. We think that different findings can be revealed in prospectively planned studies with samples to be taken before treatment in this patient group.

Another reason why no difference could be found between the groups in terms of MHR is that it is more possible to attribute meaning to subgroups with higher number of patient groups. We have previously stated that the 2nd group, in which cardiac etiology is blamed in the TOAST classification, is quite heterogeneous. Considering that the 5th group, in which the etiology could not be revealed, consists of patient groups with multiple risk factors, such as large vessel lesion and cardioembolic focus, as well as for whom no etiology could be revealed, we think that it would be useful to evaluate it from a different statistical point of view.

Other limitations of this study are that it is a single-center retrospective study and the sample size is not large enough; The dynamic trend and value of the indicator were not reflected in this study, since the dynamics and continuity of the inflammatory process and the MHR were evaluated on a single sample.

For these reasons, there is a need for more research on the relationship between MHR and stroke, and sharing positive results as well as negative results and self-criticism from an objective point of view.

Conclusion

The results we obtained in our study reveal that MHR does not show any difference between the subgroups of stroke depending on the etiology, therefore it cannot be considered as an appropriate parameter in the estimation of these subgroups, and the parameters associated with high MHR in our patient group are male gender and diabetes mellitus. There is a need for more research on the relationship of MHR to stroke subgroups and sharing positive results as well as negative results and self-criticism from an objective point of view.

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