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ASSOCIATION BETWEEN LEFT ATRIAL APPENDAGE THROMBUS FORMATION AND MONOCYTE/HDL RATIO IN PATIENTS WITH ACUTE ISCHEMIC STROKE

AKUT İSKEMİK İNME GEÇİREN HASTALARDA SOL ATRİAL APPENDAJ TROMBÜS OLUŞUMU VE MONOSİT/HDL ORANI ARASINDAKİ İLİŞKİ

Suha Cetin[1*], Mustafa Gokhan Vural[2]

[1] Okan University Hospital, Department of Cardiology, Istanbul, Türkiye. [2]29 Mayıs State Hospital, Department of Cardiology, Ankara, Türkiye.

Abstract

Objective: There is an apparent link between thrombus formation and inflammation. Monocyte/high density lipoprotein ratio has been determined as an inflammatory marker and associated with many cardiovascular disorders like coronary artery disease, acute coronary stent thrombus, coronary thrombus burden and atrial fibrillation. The aim of this study was to clarify the correlation between Monocyte/high density lipoprotein ratio and left atrial appendage thrombus formation in individuals who have suffered from an acute ischemic cerebral infarction.

Methods: The study retrospectively included a total of 69 patients who had been diagnosed with acute ischemic cerebral infarction. The patients' demographic, clinical, and echocardiographic information were gathered from their records in a retrospective manner. Monocyte/high density lipoprotein ratio and neutrophil/lymphocyte ratio were calculated from admission laboratory data.

Results: Thirteen patients had a LAATF (11 male; 64±14.5 years); 14 patients had spontaneous echo contrast stage 3 or 4 (11 male; 62.3±9.7 years) and 42 patients (29 males; 61.0±11.1 years) did not have left atrial appendage thrombus formation or SEC. With the exception of atrial fibrillation, the baseline demographic and clinical characteristics of the three groups were similar (p<0.001). Further, monocytes were significantly lower in the thrombus negative group compared to other groups (p<0.001). MHR was different in all three groups (p<0.001). This parameter was significantly increased in patients with left atrial appendage thrombus formation and spontaneous echo contrast findings.

Conclusion: Our study showed that an increased MHR is associated with left atrial appendage thrombus formation.

Keywords: Monocyte/HDL ratio; left atrial appendage; atrial fibrillation

Öz

Amaç: Trombüs oluşumu ve enflamasyon arasında kuşkusuz bir bağlantı bulunmaktadır. Monosit/yüksek yoğunluklu lipoprotein oranı bir enflamasyon göstergesi olup, koroner arter hastalığı, akut koroner stent trombozu, koroner trombüs yükü, atriyal fibrilasyon gibi birçok kardiyovasküler hastalıkla ilişkilidir. Çalışmamızın amacı akut iskemik inme geçirmiş bireylerde monosit/yüksek yoğunluklu lipoprotein oranı ve sol atriyal apendiks trombüsü arasındaki ilişkiyi değerlendirmektir.

Yöntem: Akut iskemik inme teşhisi olan toplam 69 hasta retrospektif olarak bu çalışmaya dahil edildi. Demografik, klinik ve ekokardiyografik veriler hasta dosyalarından retrospektif olarak toplandı. Monosit/yüksek yoğunluklu lipoprotein oranı ve nötrofil/lenfosit oranları hastane başvurusuna ait olan laboratuvar bulgularından hesaplandı.

Bulgular: On üç hastada sol atriyal apendaj trombüsü teşhisi konuldu (11 erkek; yaş 64,1±14,5); 14 hastada evre 3 veya 4 spontan eko kontrast saptandı (11 erkek; yaş 62,3±9,7); 42 hastada ise ne sol sol atriyal apendaj trombüsü ne de spontan eko kontrast görüntüsü mevcuttu (29 erkek; yaş 61,0±11,1). Atriyal fibrilasyon (p<0,001) haricinde 3 grup arasında demografik ve klinik bulgularda anlamlı bir fark saptanmadı. Monosit seviyesi trombüs negatif olan grupta diğer gruplara kıyasla daha düşüktü (p<0,001). Monosit/yüksek yoğunluklu lipoprotein oranı her grup için anlamlı bir fark gösterdi (p<0,001). Bu parametre sol atriyal apendaj trombüsü ve spontan eko kontrast saptanan hastalarda anlamlı yüksekti.

Sonuç: Çalışmamız yükselmiş Monosit/yüksek yoğunluklu lipoprotein oranının sol atriyal apendaj trombüsü oluşumu ile ilişkili olduğunu gösterdi.

Anahtar Kelimeler: Monosit/yüksek yoğunluklu lipoprotein oranı, sol atriyal apendiks, atriyal fibrilasyon

Corresponding author/İletişim kurulacak yazar: Süha Çetin; Okan University Hospital, Department of Cardiology, Istanbul, Türkiye. İçmeler Mah. Aydılı Yolu Cad. No:2 34947 İçmeler/Tuzla/Istanbul
Phone/Telefon: +90 0539 315 25 04 **e-mail/e-posta:** ceramos3@gmail.com
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Introduction

Cardiac thrombus embolization from the left atrium (LA) has a major impact on the etiology of ischemic stroke, especially in patients with AF.[1] The pathogenesis of thrombus formation is considered to be multifactorial and is not fully elucidated yet.[2]

Over more than one century ago Virchow suggested three abnormalities that contribute to thrombus formation: blood stasis, endothelial dysfunction, and clotting activation.[3,4] Although this triad is completely fulfilled in patients with AF, emerging evidence suggests that inflammation may also play an important role in the genesis of thrombus formation.[5-7]

Monocytes play a fundamental part in the inflammation process by secreting pro-oxidant cytokines.[8,9] High-density lipoprotein-Cholesterol (HDL-C) on the other hand has a protective effect in terms of antioxidation and also by limiting monocyte activation.[10,11] Consequently, MHR could serve as an alternative indicator of inflammation and oxidative stress and this parameter has been widely explored in the field of cardiovascular diseases.[12,13] An elevated MHR was linked to adverse outcomes. Besides, it was also an indicator of high rates of major adverse cardiovascular events such as acute thrombosis of a stent and thrombus burden in individuals with ST-segment elevation myocardial infarction (STEMI).[6,7]

The aim of this study was to elucidate the association between MHR and thrombus formation in the left atrial appendix (LAA) of patients who had suffered an AICI.

Methods

A total of 69 individuals with the diagnosis of AICI were retrospectively included in this investigation between January 2019 and June 2021.

Previous medications, anthropometric characteristics, cardiovascular history, and risk factors were obtained from the patients' medical records. The definition of arterial hypertension used in this study was a systolic blood pressure reading ≥140 mmHg and/or diastolic blood pressure reading ≥90 mmHg, as documented in at least two separate occasions.[14] The diagnosis of diabetes mellitus was based on either a fasting serum glucose concentration ≥126 mg/dl or >200 mg/dl at any testing or the use of an anti-hyperglycemic medication.[15] The criteria for dyslipidemia were derived from the 2019 European Guidelines, which defined the condition as either the use of lipid-lowering therapy or a confirmed diagnosis of dyslipidemia as documented in the patient's medical records.[16] The smoking status classification was current smoker or non-smoker. Individuals who reported using tobacco regularly in the last six months were also classified as current smokers. The definition of coronary artery disease was treated with anti-ischemic drugs, antiplatelet therapy after coronary angiography; coronary stenting performed in the past, or coronary revascularization surgery. Heart failure was considered as systolic dysfunction with an ejection fraction <50%. None of the patients had diastolic dysfunction more than grade II. Paroxysmal AF was defined as AF that resolves on its own or with intervention within one week of beginning.[17] Permanent AF was specified according to the 2020 ESC Guidelines.[17] A calculation of the body mass index (BMI; weight (kg)/ height square [m^2]) was performed on all participants.

The suspected diagnosis of AICI was verified by cranial tomographic imaging and simultaneous diffusion magnetic resonance imaging immediately after the neurological examination of the attending neurologist. Ultrasound of carotid and vertebral arteries was used to determine the etiology of AICI within one day of the occurrence. In this context, only non-complex atherosclerotic plaques without any significant stenosis have been diagnosed. The definition of noncomplex was: (a) an even and uniform surface texture and (b) homogenous and identical echocardiographic imaging or predominant echogeneity with limited territories of echolucency (<25%). Further, echocardiographic scans were conducted by a single expert examiner who was unaware of the clinical and laboratory findings. Transthoracic echocardiography examinations were performed with a commercially available ultrasound system having a 2.5-3.5 MHz transducer (ie33, Phillips Medical system, Bothell, Washington, USA). Patients lay on their left side in a resting position, and apical four-chamber and parasternal images of the LA and left ventricle (LV) were recorded. The cardiac chambers were evaluated using echocardiographic images, and the following parameters were measured: The modified Simpson's method was utilized to determine the ejection fraction of the LV.[18] To calculate the LA volumes, the area-length technique was employed from the apical four and two-chamber views at end-systole, which was just before the opening of the mitral valve. The LA volume index was computed by dividing the LA volumes by the body surface area.[19] In the apical four-chamber view, pulsed-wave Doppler of trans-mitral LV inflow was conducted, with the sample volume positioned at the level of the mitral tips. Tissue Doppler mitral annular velocity was ascertained from the four-chamber view by positioning the sample volume on the lateral annulus, close to the insertion site of the mitral valve.[20] The LV diastolic function was evaluated by measuring peak early (E) and early diastolic mitral annular velocity (E'). To determine the LV filling pressures, the E/E' ratio was employed as an index.

All patients also underwent 2-and 3-dimensional transesophageal echocardiography (TEE) (ie33, Phillips, or Vivid I, GE Healthcare) within three days of the AICI occurrence. Various images of the LAA were acquired using different perspectives, including a continuous sweep between 0 and 180 degrees in both short and long-axis views, which were taken from the mid-esophageal position. The observation of LAATF (an intra-cavity mass identified and characterized as uniformly echo-dense and well-defined, clearly separate from the surrounding endocardium and pectinate muscles, and

visible in multiple image planes) was recorded and the peak velocity at which the LAA empties (utilizing a Pulse wave Doppler placing the probe one cm deep into the appendage's orifice) determined.[21] The visibility of SEC was enhanced by adapting the gain settings to eliminate low-amplitude echo images, thus improving image clarity. SEC severity was evaluated none, when there was no smoke-like echogenicity present; stage 1 was defined as small amount of echogenicity observed in the LAA or sparsely dispersed in the main LA; stage 2 was a more concentrated whirling configuration than stage 1 was observed, along with SEC distributed in a comparable pattern; stage 3 was documented, when throughout both the main LA and the LAA, a concentrated whirling configuration was noted; and stage 4 finally, showed a more significant echo density and the whirling configuration was very slow, surpassing stage 3 in intensity .[22] All cardiac imaging was initiated upon request of the neurology department of our hospital.

Blood samples were obtained from an antecubital vein by venous needle puncture after a 12-hour fast. We used blood samples taken the next morning after the admission date of the patients. A commercially available automated hematology analyzer (Sysmex XT-1800i, Kobe, Japan) that provided complete blood count was utilized for computing hemoglobin, white blood cell, neutrophil, lymphocyte and platelet values. Further, the levels of biochemical markers in the blood, such as baseline lipid profile, creatinine and plasma glucose, were measured to assess the metabolic state of the subjects. These parameters were calculated using an auto-analyzer (Abbot Architect ci4100, Holliston, MA, USA). MHR was obtained by dividing the number of monocytes by HDL cholesterol level. The value of NLR was determined by dividing the number of neutrophils by the number of lymphocytes present in the blood.

The criteria for exclusion from the study were established as follows: Decompensated heart failure; congenital or pulmonary disease or critical valve dysfunction; patients with prosthetic valves; renal or hepatic dysfunction; clinical evidence of cancer; blood dyscrasiasis; auto-immune diseases; acute or chronic infections or inflammatory conditions; current therapy with corticosteroids and/or non-steroidal anti-inflammatory drugs.

The research protocol adhered to the principles outlined in the Declaration of Helsinki and received approval from the Institutional Ethics Committee of Istanbul Okan University (No: 23.06.2021; 139/24)

Statistical Analysis

Statistical evaluation of the obtained data was done with SPSS for Windows 11.5 (Chicago, INC). To compare continuous data between the three groups, One-way ANOVA and Bonferroni tests were used, and for comparing qualitative data, the Chi-Square test was employed. The statistical significance boundary was accepted as 0.05.

Results

This study included 69 patients who had been diagnosed with AICI. The participants were categorized into three groups based on the presence or absence of LAATF and SEC.

Table 1 displays the baseline characteristics of the study sample. The age and gender distribution of the patients did not differ significantly. Body mass index, systolic and diastolic blood pressure were comparable. Smoking habits, chronic diseases, and use of medication did not show any statistical significance. Patients with AF had statistically significant more LAATF than patients with normal sinus rhythm.

Table 1. Basic characteristics of the study population

Parameters	Thrombus (+) n=13	SEC stage 3-4 n=14	Thrombus (-) n=42	p-Value
Age (mean±SD)	64.1±14.5	62.3±9.7	61.0±11.1	0.688
Male	11(84.6%)	11(78.6%)	29(69.0%)	0.485
NSR	2(15.4%)	11(78.6%)	28(66.7%)	0.001
PAF	2(15.4%)	2(14.3%)	11(26.2%)	0.001
AF	9(69.2%)	1(7.1%)	3(7.1%)	0.001
BMI (mean±SD)	29.4±1.2	30.2±1.5	29.8±1.5	0.367
SBP (mean±SD)	137.6±12	138.2±6.6	133.3±9.5	0.205
DBP (mean±SD)	89.2±8.6	94.2±12.3	94.4±11.7	0.346
CAD	7(53.8%)	8(57.1%)	18(42.9%)	0.579
Heart failure	5(38.5%)	8(57.1%)	19(45.2%)	0.606
Smoking	7(53.8%)	7(50.0%)	21(50.0%)	0.969
Diabetes	3(23.8%)	2(14.5%)	12(28.6%)	0.556
AHT	5(38.5%)	6(42.9%)	22(52.4%)	0.624
AHTM	5(38.5%)	6(42.9%)	22(52.4%)	0.624
BB/CCB	6(46.2%)	6(42.9%)	15(35.7%)	0.757
ATM	7(53.8%)	8(57.1%)	17(40.5%)	0.465
ALM	7(53.8%)	8(57.1%)	14(33.3%)	0.186

SEC, spontaneous echo contrast; NSR, normal sinus rhythm; PAF, paroxysmal atrial fibrillation; AF, atrial fibrillation; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; CAD, coronary artery disease; AHT, arterial hypertension; AHTM, antihypertensive medication; BB, beta-blocker; CCB, calcium channel blocker; ATM, antithrombotic medication; ALM; antilipidemic medication

Comparison of the laboratory findings are represented in Table 2. In contrast to other groups, the Thrombus (-) group exhibited significantly lower levels of monocytes. All other laboratory parameters did not demonstrate any significant differences between the groups.

Table 2. Laboratory findings of the study population

Parameters	Thrombus (+) n=13	SEC stage 3-4 n=14	Thrombus (-) n=42	p-value
Hgb g/dl)	14.4±1.51	14.2±1.73	13.8±1.75	0.75
WBC (10^9/L)	8.6±1.7	9.8±2.5	9.1±1.6	0.62
Neutrophiles (10^3 /μl)	9.2±3.5	8.3±1.2	8.7±2.1	0.70
Lym(10^3 /μl)	3.5±1.4	2.8±2.1	3.2±1.2	0.72
Monocytes (10^3 /μl)	0.83±0.36	0.81±0.24	0.64±0.3	0.001
Platelets (10^3 /μl)	269.5±84.6	254.5±70.2	256.3±75.3	0.28
Triglyceride (mg/dl)	197.9±50.7	195.5±83.1	197.5±54.7	0.90
HDL (mg/dl)	39.8±9.7	39.6±9.5	38.8±7.3	0.92
LDL (mg/dl)	130.0±34.5	129.9±53.7	131.8±41.2	0.19
Glucose (mg/dl)	126.2±52.8	127.7±42.1	119.7±37.3	0.08
Creatinine (mg/dl)	1.01±0.4	0.97±0.3	1.03±04	0.3

SEC, spontaneous echo contrast; WBC, white blood cells; HDL, high density lipoprotein; LDL, low density lipoprotein; Hgb, hemoglobin; Neu, Neutrophiles; Lym, Lymphocytes

Table 3 displays MHR, NLR, and echocardiographic findings of the study sample. A significant difference was observed between the three groups with regards to MHR ($p<0.001$ between the groups). NLR levels were comparable between Thrombus (+) and SEC group. But in comparison to other groups, it was statistically reduced in the Thrombus (-) group. LAA Ev showed statistically significant difference between all groups: Thrombus (+)-SEC: $p<0.008$; Thrombus (+)-Thrombus (-): $p<0.001$; SEC-Thrombus (-): $p<0.001$).

Table 3. MHR, NLR and echocardiographic findings of the study population

Parameters (mean±SD)	Thrombus (+) n:13	SEC stage 3-4 n:14	Thrombus (-) n:42	p-value
MHR	0.59±0.24	0.45±0.20	0.22±0.09	<0.001
NLR	7.9±6.0	6.8±4.6	3.4±3.8	0.002
LVEF	45.9±10.4	41.8±9.5	46.0±7.8	0.40
LAVI	43.8±7.1	43.3±3.9	42.7±2.2	0.86
E/E'	13.4±3.3	13.3±3.9	12.7±2.2	0.72
LAA Ev	26.0±7.7	28.8±8.3	34.8±9.0	0.004

SEC, spontaneous echo contrast; MHR, monocyte to high-density lipoprotein cholesterol ratio; NLR, neutrophil to lymphocyte ratio; LVEF, left ventricular ejection fraction; LAVI, left atrial volume index; LAA Ev, left atrial appendix emptying velocity.

Discussion

One of the primary results of this research was that patients who had a LAATF demonstrated a considerably higher MHR value. Further, a significant correlation was found between MHR and NLR. As far as we are aware, this is the initial study that highlights the connection between MHR and LAATF.

Monocytes have a crucial impact on the progression of chronic inflammation and cardiovascular disorders by modulating inflammatory cytokines and adhesion molecules.[23] These prooxidant cytokines are promoting coagulation and inhibit fibrinolysis.[24] HDL-C on the other hand has some cardioprotective effects improving endothelial function via its anti-inflammatory and antioxidative effects.[25] HDL-C inhibits the transmigration of monocytes into the endothelium and prevents monocyte activation.[26] Therefore, it seems to be reasonable to use MHR as an inflammation parameter by proportioning these two markers.

In many studies, MHR and NLR were found to be important vascular inflammatory markers and reliable predictors for atherosclerosis formation and also for cardiovascular outcomes.[27] In one study for example Avci et al. investigated the effectiveness of MHR in 269 patients with the diagnosis of pulmonary embolism for predicting in-hospital mortality. Here, compared to the group without mortality, the group that experienced mortality had significantly higher MHR values.[28] Another investigation by Isik et al. revealed that patients with angiographically isolated coronary artery ectasia had significantly elevated NLR values when compared to patients with normal coronary angiograms. They concluded a strong association between increased NLR values and the occurrence of isolated coronary artery ectasia.[29]

The main focus of the current research was on investigating the correlation between LAATF and MHR which is considered relevant marker of inflammation. Virchow suggested more than a century ago that the formation of a thrombus requires the presence of three conditions: Flow disturbances, endothelial dysfunction, and clotting activation.[30] Since most of our patients with LAATF had AF, the mentioned Virchow triad is fulfilled in many aspects: The absence of atrial systole leads to stagnation of blood within the LA, which can be seen on transesophageal echocardiography as SEC.[31] Further, in our study individuals with LAATF or SEC had a substantial reduction in LAA ejection velocity compared to patients without LAATF underlining this flow abnormality. Endothelial dysfunction is also detected in patients with AF. Numerous studies have verified this by evaluating various markers of endothelial dysfunction, including von Willebrand factor (vWF) and E-selectin.[32] Finally, abnormal changes in coagulation are also present. Many investigations have demonstrated an elevation in serum concentrations of F1+2, fibrinogen, and D-dimer in patients with AF.[33] But still, the pathophysiology of thrombus formation in patients with AF remains multi-factorial and the precise mechanisms by which this might occur are uncertain.[2] Increasing evidence suggests that inflammation may contribute to this hypercoagulable state as well.[34] Studies have shown that plasma levels of C-reactive protein (CRP) and interleukin-6 are linked to thrombotic state in patients with AF.[35] CRP is also associated with SEC formation in LA or LAA.[36] Further, one investigation demonstrated elevated expression of vWF in the endocardium of patients with AF with correlation to adherent platelet thrombus formation.[37] Thrombosis can be induced by inflammation through a mechanism that involves vWF-mediated process such as endothelial activation, the release of vWF, and the formation of hyper adhesive vWV strands and fibrils.[38]

Nakamura et al. demonstrated in one study high expression of tissue factor in the LA endocardium showing that local inflammation is involved in the genesis of thrombus.[39] Of note, two of our patients with normal sinus rhythm and elevated MHR values had a thrombus formation in the LAA, too. This may suggest that not only the classical triad of Virchow is responsible for thrombus formation in the LAA. Inflammation of the endocardium with generation of a prothrombotic state even in non-AF patients may contribute to thrombus formation. In this context, MHR may indicate this prothrombotic state of the LA endocardium due to local inflammation. Yamashita et al. found that monocytes and macrophages within atrial specimens of patients with AF expressed cytokines leading to an 'occult myocarditis' with further recruitment of monocytes and macrophages.[40] Arisoy et al demonstrated the association between MHR and the extent of thrombus formation in patients with STEMI.[5] A total of 414 individuals diagnosed with STEMI were included in the study population. The participants were classified into two categories based on the extent of thrombus formation by performing a primary percutaneous coronary intervention (PCI). MHR values were significantly elevated in the group with a high extent of thrombus formation. Another study by Cetin et al. showed that MHR predicts stent thrombosis after PCI in patients who were followed up for 37.2 months. During this period of time 112 patients developed stent thrombosis. Here MHR was an independent predictor of stent thrombosis in this patient group.[6] These studies reveal that a pro-inflammatory state of the endothelium seems to play an important role in the genesis of thrombus formation demonstrated by the inflammation-marker MHR.[41] Additionally, in our study MHR values were also significantly increased in patients with SEC stage 3 and 4 compared to patients without any thrombus in the LAA. This again underscores the inflammatory milieu. In one study Maehema et al. investigated inflammation and formation of thrombus in the LA of individuals with non-rheumatic AF. They enrolled 190 patients with non-rheumatic AF who underwent a TEE examination. All participants were examined for the existence or non-existence of LAATF via the above-mentioned method. Additionally, CRP values of the study population were measured. They found that systemic inflammation, represented by elevated CRP levels, was related to thrombus formation in this patient group. Further, they concluded that this prothrombotic state, in addition to the Virchow triad, may be associated with SEC.[4]

Our study should be evaluated with its inherent limitations. To begin with, this study is retrospective in nature and has a relatively small sample size. Further, the occurrence of LAATF in individuals who recently suffered from an embolic event may have been underestimated due to the possibility of LAATF being previously embolized and thus not detected. Finally, other inflammation markers such as sedimentation, C-Reactive Protein or high-sensitive C-Reactive Protein were not included in this study due to lack of data.

In Conclusion, this study focused on the relationship between MHR and LAATF. MHR is considered a novel biomarker representing both inflammation and oxidative stress. Thus, it appears that inflammation has a significant impact on the occurrence of LAATF. Based on our findings, additional prospective investigations with a more extensive participant pool would yield more comprehensive insights.

Compliance with Ethical Standards

The research protocol adhered to the principles outlined in the Declaration of Helsinki and received approval from the Institutional Ethics Committee of Istanbul Okan University (No: 23.06.2021; 139/24)

Conflict of Interest

The authors declare no conflicts of interest.

Author Contribution

Authors contributed equally to this work.

Financial Disclosure

Financial disclosure none.

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