Peripheral Blood Cell Profile and Monocyte HDL Ratio in Alzheimer's Disease: A Hospital-Based Case-Control Study

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Research Article

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Abstract

Background: The monocyte/HDL-C ratio (MHR) has emerged as a new marker of inflammation in recent years. The purpose of this research was to examine the distinction of MHR between individuals with Alzheimer's disease (AD) and healthy individuals, and to assess its feasibility as a straightforward and easily computable biomarker for evaluating the severity of the disease.

Methods: A retrospective study was conducted with 184 subjects admitted for various reasons at the Neurology Outpatient Department of Giresun University Faculty of Medicine. The hospital's electronic patient record data between September 2021 and April 2022 were screened.

Results: Individuals diagnosed with AD were classified into three subgroups based on the progression of the disease: mild, moderate, and severe. MHR was higher in the moderate and severe dementia subgroups compared with the controls according to subgroup analysis (***P*=**0.013). An increase in MHR was found in patients with AD. The multivariate logistic regression analysis model revealed that a one-unit increase in MHR resulted in 1.081 times increase in the risk of AD (OR: 1.081 (CI: 1.005-1.162; ***P*=** 0.035).

Conclusion: This is the first study in the literature exhibiting an increased MHR value in AD. High MHR values in the late stages of the disease demonstrate a potential for MHR to predict the prognosis. It might be a marker reflecting increased cardiovascular risk and an unfavorable prognosis in patients with AD.

Introduction

Cognitive and cerebrovascular diseases constitute some of the most common neurological disorders. They can impede daily activities and deteriorate quality of life, particularly among the elderly. [1]. Alzheimer's disease (AD) is the most widespread neurodegenerative disorder, characterized by a gradual decline in memory and cognitive abilities. It is more frequently encountered in the elderly and severely affects daily activities [2]. AD is found in 69% of dementia patients over 75 years of age and is characterized by an impairment in the activities of daily living, cognitive deterioration, and behavioral disorders [1].

Histopathological abnormalities can be observed in the early stages of AD, years before the clinical symptoms related to dementia. AD has already entered a histopathologically advanced stage at the time such symptoms actually appear [3]. Early diagnosis and treatment are important in slowing down disease progression. Easily accessible biomarkers are critical for the early diagnosis of AD.

The monocyte/HDL-C ratio (MHR, found by dividing the absolute monocyte value by the absolute High-Density Lipoprotein-cholesterol (HDL-C) value) is a new inflammation marker demonstrated to have a strong association with cardiovascular events [4]. Monocytes develop from progenitor cells in the bone marrow and released into the circulation where they migrate to tissues and release various proinflammatory cytokines in the inflammation zone. They are therefore accepted as biomarkers for detecting the severity of inflammation and are the main source of proinflammatory cytokines [5],[6]. Macrophages stimulate the production of p-tau and amyloid precursor, leading to neuronal degeneration [7].

Monocytes interact with the damaged activated endothelium, playing an important role in atherosclerosis progression. They also accelerate the development of atherosclerosis by increasing the expression of proinflammatory cytokines such as monocyte chemotactic protein 1, vascular cell adhesion molecule 1, and intercellular adhesion molecule 1. On the other hand, HDL-C suppresses macrophage activation, Low-Density Lipoprotein-cholesterol (LDL-C) oxidation, and macrophage migration with its antioxidant and anti-inflammatory effects. HDL-C inhibits the production of endothelial adhesion molecules while suppressing the differentiation of monocytes to macrophages and their migration and activation. HDL-C also increases endothelial nitric oxidase expression and induced vasorelaxation. HDL-C has an antioxidant effect to protect endothelial function [8],[9].

MHR could reflect the inflammatory condition and has been associated with chronic inflammation related to disease progression. Increased monocyte count and a decreased HDL-C serum level have been associated with the progression of inflammation. Therefore, MHR emerges as an inflammatory marker and it is also a prognostic marker for cardiovascular diseases [10].

The objective of this study was to examine the variation of MHR between AD patients and healthy individuals, and to investigate its suitability as a straightforward and easily calculable biomarker for determining the progression of the disease.

Material Method

Subjects: A retrospective study was conducted with 184 subjects who presented for various reasons to the Neurology Outpatient Department of Giresun University Faculty of Medicine. The hospital's electronic patient record data between September 2021 and April 2022 were screened. Patients with AD according to the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria made up the patient group, and cases who had presented at the neurology outpatient departments for nonspecific symptoms and had not been diagnosed with dementia made up the control group **[11].** The patient group was divided into three groups according to the Clinical Dementia Grading scale (CDR) as mild, moderate, and severe. Global cognitive function of all subjects was evaluated using the Mini-Mental State Examination (MMSE). The control group subjects were older than 65 years and fully independent as regards the activities of daily living.

Laboratory analysis: Baseline information including age, sex, and comorbidities was collected. The blood or serum glucose, total cholesterol, triglyceride, HDL-C, LDL-C, and uric acid levels were evaluated with the COBAS 8000 series (Switzerland) following 8 hours of overnight fasting. White blood cell measurement was done with the automated hematology analyzer MINDRAY BC 6800 (China). The blood monocyte count was divided by the blood HDL-C level to calculate the monocyte count to HDL-C ratio.

The following exclusion criteria were used: 1- The presence of hematologic or oncologic diseases or chronic renal or liver failure; 2- Being on antihyperlipidemic medication; 3- AD mimics; 4- non-Alzheimer's dementia; 5- Rheumatological disorders; 6-Inflammatory bowel disorders; 7- Hypothyroidism or hyperthyroidism; 8- Any kind of infection in the last month according to the hospital records; 9- Any minor or major surgical procedure or intervention during the past month.

The Ordu University Ethics Committee for Clinical Research granted approval for the study.

Statistical analysis: The IBM SPSS v23 software was used to analyze data. Normal distribution was determined with the Kolmogorov-Smirnov and Shapiro-Wilk tests. Pearson's chi-square test was used for evaluating categorical variables. Group pairwise comparison was with the t-test and the Mann-Whitney U-test for normally and non-normally distributed data, respectively. Comparisons among three or more groups were conducted using one-way variance analysis and Duncan test for normally distributed data and Kruskal-Wallis H test and Dunn test for non-normally distributed data, respectively. Risk factors that could have an effect on Alzheimer's disease were analyzed with the binary logistic regression model. Pearson's correlation coefficient and Spearman's rho correlation coefficient were used to analyzing the relationship between normally and non-normally distributed quantitative data, respectively. Adjustment for confounding factors was with multivariate logistic regression models. The model was adjusted for age, sex, and the monocyte/HDL ratio; the glucose, uric acid, triglyceride, and hemoglobin levels; and comorbidities. Statistical significance was set at $P<0.05$.

Results

A total of 81 healthy individuals and 103 individuals diagnosed with AD were included in the study. The gender distribution was 33 males and 70 females in the AD group while the respective numbers were 30 and 51 for the control group. The mean age was 81.88 ± 5.19 and 81.57 ± 5.39 years in the AD and control groups, respectively. The groups showed no difference as regards sex and age (P **= 0.478;** P **= 0.688**). Diabetes mellitus was more commonly observed in the control group. Arterial hypertension was more common in the AD group and also the most commonly observed comorbidity in this group (**n = 54; 52.4%**), but there was no statistical significance (P **= 0.64**) (Table 1). There was also a lack of statistically significant difference between the groups based on comorbidities (P = 0.640). (Table 1). The MHR value was found to be significantly higher in the AD group compared to the control group, with a statistical significance of (P = 0.013). Serum uric acid, total cholesterol, triglyceride, HDL-C, and LDL-C values were similar between the groups (Table 2). The MMSE score was significantly lower in the Alzheimer group when compared to the control group (P < 0.001) (Table 2).

The AD patients were classified into three subgroups based on the progression of the disease: mild (n = 23), moderate (n = 48), and severe (n = 32). A statistically significant difference was observed among these subgroups in terms of the MMSE score. The MMSE scores were significantly lower in the severe dementia subgroup (P = 0.001). Subgroup analysis was performed with Kruskal-Walli's test. The MHR values of the moderate and severe AD subgroups were significantly higher than the control group (P **= 0.012) (**P **= 0.035)** (Fig. 1). The blood monocyte count was higher in the moderate severity dementia subgroup compared to the control group (P **= 0.003**).

A weak but statistically significant negative correlation was found between the MHR and MMSE scores (r=-0.191; P = 0.009). The MHR values were also negatively correlated with the MCHC, with moderate power (**r=-0.324;** P **< 0.001**). A weak positive correlation was found between the MMSE score and the Red Blood Cell (RBC) count (**r = 0.175;** P **= 0.018**) (Table 3).

A logistic regression model was established to examine the impact of risk factors on AD. In the univariate model, MHR was not found to have an effect on AD development (**OR: 1.066 (CI: 0.998–1.138);** P **= 0.056**). The multivariate logistic regression analysis model revealed that a one-unit increase in MHR resulted in a 1.081 times increase in the risk of AD (**OR: 1.081 (CI: 1.005–1.162);** P **= 0.035**). Also, an one-unit increase in the serum glucose level gave rise to a 1.008 times increase in the AD risk (**OR: 1.008 (CI: 1.001–1.016);** P **= 0.034**). The risk factors analyzed in the regression model are presented in table (Table 4).

Discussion

An increase in MHR has been found in AD patients in the current study, and this increase was correlated with the MCHC and MMSE values. This is the first study in the literature to report an increased MHR value in AD.

Various peripheral blood parameters have been studied in inflammatory disorders and also in AD [12],[13]. The platelet distribution width has been found to correlate with an increased rate of mild cognitive impairment in AD cases. The neutrophil and lymphocyte ratios have shown to be increased in AD patients as peripheral blood biomarkers [14]. Another biomarker, the mean platelet volume (MPV), was significantly increased in AD, and its value correlated with the severity of cognitive impairment [15].

Recent data has shown that increased MHR reflects the severity of various disease states such as endothelial dysfunction in Behcet's disease, metabolic syndrome, myocardial infarction, and aortic aneurysm [9], [16], [17]. Mirza et al. have shown increased MHR to be an inflammatory marker in patients with pseudoexfoliation syndrome and glaucoma [18].

MHR has recently emerged as a new and reliable candidate marker for diabetic complications [19]. Diabetes mellitus is also a risk factor for AD [20]. Higher MHR values have been observed in patients with diabetic nephropathy, and MHR has been suggested as a marker for this condition [19]. The frequency of DM in the current study was not statistically different between the AD subgroups, taking disease severity into account. This might be due to the limited number of cases in the study.

MHR has also been investigated Parkinson's disease patients. Although no difference was observed with the control group, the MHR was higher in Parkinson patients with long-term follow up [21]. MHR stands out as a marker reflecting inflammatory and oxidative stress in Parkinson's disease, similar to the neurodegenerative disorder AD, but has not been shown to be a marker early disease diagnosis as it is higher in patients followed for a longer time. Although

MHR was increased in the AD patients compared to the control group in the current study, the reason was a larger increase in the intermediate and advanced stage patients than those in the early stages on subgroup analysis.

A significant positive correlation was discovered between the RBC value and MMSE in the severe AD group.

A decreased hemoglobin level might be another blood parameter related to AD. It likely impacts cognitive function by decreasing cerebral blood perfusion, leading to neuroinflammation and oxidative stress. [22].

MHR is also a highly predictive marker for cardiovascular disorders. It is closely related to inflammation and is thought to be a marker for atherosclerosis development [23]. Many recent articles have reported increased MHR in atherosclerotic vascular events to be a prognostic marker. MHR has also been reported to be increased in acute ischemic stroke and to be associated with an increased mortality rate [24].

Atherosclerosis or vascular problems may be encountered more commonly in advanced stage AD patients. However, the high MHR values in the late stages of the AD demonstrate a potential for MHR to predict the prognosis as in coronary artery disease [25]. Based on studies in the literature showing a linear relationship between AD severity and vascular inflammation, it is possible that vascular changes caused by changes in MHR are an indicator of an unfavorable prognosis [26].

The limitations of this study include its retrospective design and the absence of data on factors such as smoking, alcohol consumption, body mass index, arterial blood pressure, and levels of inflammatory markers (such as interleukin-6, CRP, and tumor necrosis factor alpha). Neuropsychological tests (Letter Digit Substitution Task, Word Fluency Test, Stroop test, 15-word Verbal Learning Test, and Purdue Pegboard Test) have not been performed in the study population.

In conclusion, MHR could not be used as a diagnostic test for AD but it might be a marker reflecting increased cardiovascular risk and an unfavorable prognosis. Investigating the vascular risks when MHR value measurement, an easily accessible and non-invasive method, gives high values in AD patients could be recommended. This would enable early prevention of potential vascular events that could increase morbidity and mortality in AD. More extensive studies with a larger scope are needed to demonstrate any such relationship in a more robust manner.

Table 1
Gender and comorbidity distribution by group

	Alzheimer's Disease N (%)	Control N (%)	*P* value*
Gender			
Male	33 (32)	30 (37)	0.478
Female	70 (68)	51 (63)	
Comorbidity			
Absent	15 (14.6)	17 (21)	0.64
DM	5 (4.9)	7 (8.6)	
HT	54 (52.4)	41 (50.6)	
Stroke	1 (1)	1 (1.2)	
DM + HT	22 (21.4)	13 (16)	
HT + Stroke	5 (4.9)	2 (2.5)	
DM + HT + Stroke	1 (1)	0 (0)	
*Pearson chi-square test, N: number, HT: Hypertension, DM: Diabetes mellitus			

Table 2
Demographic and laboratory parameters

Variable*	Alzheimer's Disease	Control	*P* value
Age, mean ± SD	81.88 ± 5.19	81.57 ± 5,39	0.688
Uric Acid, mean ± SD	5.13 ± 1.45	5.14 ± 1.39	0.950
MMSE score, median (range)	14 (0–24)	26 (25–30)	**< 0.001**
Monocytes, median (range)	0.48 (0.15–0.95)	0.39 (0.19–0.83)	**0.001**
HDL-C, median (range)	48 (22–101)	50 (25–90)	0.544
MHR, median (range)	10 (3.12–30.71)	8.16 (2.64–28.62)	**0.013**
LDL-C, mean ± SD	119.99 ± 36.69	121.43 ± 33.6	0.784
Cholesterol mean, ±SD	197.46 ± 43.07	197.4 ± 41.49	0.992
Triglyceride, median (range)	126 (41–584)	117 (51–626)	0.918
Glucose, median (range)	104 (83–471)	104 (75–386)	0.432
MCV, median (range)	90.4 (71.1–107.1)	88.3 (63.9–109.1)	0.136
MCHC, median (range)	33.2 (2.3–35.3)	33.3 (30.9–38.9)	0.076
HGB, mean ± SD	12.67 ± 1.53	12.92 ± 1.45	0.259
RBC, mean ± SD	4.28 ± 0.52	4.41 ± 0.47	0.069

MMSE: Mini-Mental Test State Examination, HDL-C: High-Density Cholesterol, LDL-C: Low-Density Cholesterol, MCV: Mean Corpuscular Volume, HGB: Hemoglobin, RBC: Red Blood Cell, MCHC: Mean Corpuscular Hemoglobin Concentration, MHR: Monocyte HDL-C Ratio, SD: Standard Deviation

* Mean ± standard deviation has been used for normally distributed data, and median (min-max) for non-normally distributed data.

Table 3
Regression analysis of the quantitative data

		Age	MMSE	Monocytes	HDL-C	MHR	LDL-C	Cholesterol	Triglyceride	Glucose	MCV	MCHC	
MMSE score	r	-0.138**											
	p	0.061											
Monocytes	r	0.077**	-0.214**										
	p	0.296	**0.004**										
HDL-C	r	-0.080**	0.070**	-0.190**									
	p	0.279	0.343	**0.010**									
MHR	r	0.124**	-0.191**	0.804**	-0.696**								
	p	0.095	**0.009**	**< 0.001**	**< 0.001**								
LDL-C	r	-0.098*	0.050**	-0.061**	0.105**	-0.109**							
	p	0.185	0.499	0.413	0.157	0.142							
Cholesterol	r	-0.148*	0.080**	-0.117**	0.250**	-0.231**	0.886*						
	p	**0.044**	0.279	0.113	**0.001**	**0.002**	**< 0.001**						
Triglyceride	r	-0.070**	0.078**	0.038**	-0.381**	0.259**	0.120**	0.259**					
	p	0.348	0.293	0.606	**< 0.001**	**< 0.001**	0.106	**< 0.001**					
Glucose	r	-0.121**	-0.073**	0.032**	-0.049**	0.057**	-0.056**	-0.040**	0.152**				
	p	0.102	0.326	0.670	0.513	0.442	0.448	0.590	**0.039**				
MCV	r	0.037*	-0.116**	-0.190**	0.001**	-0.111**	-0.088*	-0.126*	-0.114**	0.011**			
	p	0.614	0.117	**0.010**	0.986	0.134	0.237	0.089	0.122	0.884			
MCHC	r	-0.169**	0.099**	-0.353**	0.149**	-0.324**	0.065**	0.110**	-0.118**	0.029**	0.208**		
	p	**0.022**	0.182	**< 0.001**	**0.044**	**< 0.001**	0.383	0.137	0.112	0.699	**0.005**		
HGB	r	-0.219**	0.135**	-0.131**	0.048**	-0.137**	0.145**	0.161**	0.022**	-0.007**	0.210**	0.422**	
	p	**0.003**	0.067	0.077	0.518	0.064	0.050	**0.029**	0.762	0.922	**0.004**	**< 0.001**	
RBC	r	-0.207*	0.175**	0.099**	-0.028**	0.053**	0.242*	0.242*	0.100**	-0.062**	-0.400*	0.033**	
	p	**0.005**	**0.018**	0.184	0.709	0.480	**0.001**	**0.001**	0.181	0.405	**< 0.001**	0.658	

*Pearson's correlation coefficient **Spearman's rho correlation coefficient

MMSE: Mini-Mental Test State Examination, HDL-C: High-Density Cholesterol, LDL-C: Low-Density Cholesterol, MCV: Mean Corpuscular Volume, HGB: Hemog
RBC: Red Blood Cell, MCHC: Mean Corpuscular Hemoglobin Concentration, MHR: Monocyte HDL-C Ratio

Table 4
Logistic regression analysis of the risk factors

	Multivariate		
	OR*	95% CI**	*P* value
Age	1.006	(0.946–1.069)	0.853
Gender (Reference: Male)	1.283	(0.638–2.58)	0.484
Uric Acid	0.951	(0.758 – 0.194)	0.667
MHR	1.081	(1.005–1.162)	**0.035**
Triglyceride	0.998	(0.994–1.002)	0.351
Glucose	1.008	(1.001–1.016)	**0.034**
Comorbidity			
DM	0.445	(0.101–1.965)	0.285
HT	1.531	(0.66–3.547)	0.321
Stroke	1.487	(0.079–27.893)	0.791
DM + HT	0.907	(0.263–3.124)	0.877
HT + Stroke	2.249	(0.357–14.17)	0.388
DM + HT + Stroke	—	—	—
HGB	0.924	(0.74–1.155)	0.488

OR: Odds ratio, CI: Confidence interval, **HT**: Hypertension, **DM**: Diabetes mellitus, **MHR**: Monocyte HDL-C Ratio, **HGB**: Hemoglobin

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Figures

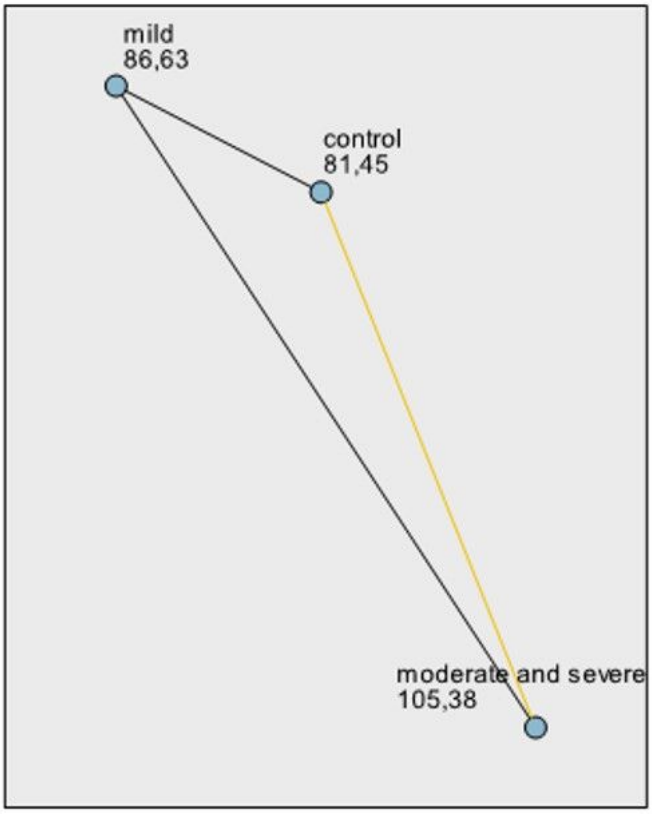

Figure 1

Pairwise comparisons of disease severity

Each node shows the sample average rank of disease severity