Peripheral Blood Cell Profile and Monocyte–High-density Lipoprotein Ratio in Alzheimer's Disease: A Hospital-based Case-control Study

Keywords
Alzheimer's disease, Monocyte HDL ratio, Mini-Mental Test State Examination

Abstract

Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by a progressive decline in memory and cognitive abilities. 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 MHR alterations in AD and to assess its feasibility as a straightforward and easily computable biomarker for evaluating the severity of the disease.

Material and methods

A retrospective case-control study was conducted with 101 patients with AD and 81 age and sex-matched controls from the hospital records. AD was diagnosed according to the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria. The hospital's electronic patient record data between September 2021 and April 2022 were screened.

Results

Individuals diagnosed as having 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 a 1.081 times increase in the risk of AD (OR: 1.081, 95% CI: [1.005-1.162]; P= 0.035).

Conclusions

High MHR values could not be used as a diagnostic test for AD. Instead, because it negatively correlates with MMSE, it could be a good index reflecting the increased AD risk and disease severity.

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Running title: The monocyte-HDL ratio in Alzheimer's disease

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Background: Alzheimer's disease (AD) is a neurodegenerative disorder characterized by a progressive decline in memory and cognitive abilities. 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 MHR alterations in AD and to assess its feasibility as a straightforward and easily computable biomarker for evaluating the severity of the disease.

Methods: A retrospective case-control study was conducted with 101 patients with AD and 81 age and sex-matched controls from the hospital records. AD was diagnosed according to the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria. The hospital's electronic patient record data between September 2021 and April 2022 were screened.

Results: Individuals diagnosed as having 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 a 1.081 times increase in the risk of AD (OR: 1.081, 95% CI: [1.005-1.162]; ***P***= 0.035).

Conclusion: High MHR values could not be used as a diagnostic test for AD. Instead, because it negatively correlates with MMSE, it could be a good index reflecting the increased AD risk and disease severity.

Keywords: monocyte HDL ratio; Alzheimer's disease; Mini-Mental Test State Examination

Introduction:

Cognitive disorders such as Alzheimer's disease (AD) constitute the most common neurologic disorders. They can impede daily activities and deteriorate the quality of life, particularly among the elderly **[1]**. 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]**, **[3].** AD is found in 69% of patients with dementia aged over 75 years and is characterized by an impairment in activities of daily living, cognitive deterioration, and behavioral disorders **[1].**

Histopathologic abnormalities such as amyloid plaque aggregation, neurofibrillary tangles, and oligodendroglial hypertrophy can be observed in the early stages of AD, years before the clinical symptoms related to dementia present **[4]**. AD has already entered a histopathologically advanced stage at the time such symptoms appear **[5].** Early diagnosis and treatment are important in slowing down disease progression. Easily accessible biomarkers are critical for the early diagnosis of AD.

Platelet distribution width, the neutrophil to lymphocyte ratio (NLR), mean platelet volume (MPV), and granulocyte to lymphocyte ratio (GLR) have been examined in the literature **[6], [7], [8].** Peripheral inflammation as measured using NLR, red cell distribution width (RDW), and MPV, is associated with poor cognitive function and brain aging **[9]**. MHR could reflect an inflammatory condition and has been associated with chronic inflammation related to disease progression. Increased monocyte counts and decreased high-density lipoprotein-cholesterol (HDL-C) serum levels have been associated with the progression of inflammation and oxidative stress. The monocyte/HDL-C ratio (MHR, found by dividing the absolute monocyte value by the absolute HDL-C value) is inflammation marker demonstrated to have a strong association with cardiovascular events **[10].**

Sun et al. reported that monocytes might be an annihilator for Tau proteins in AD **[11].** Activated monocyte-related damage in the blood-brain barrier is another reason for the development of AD **[12].** Monocytes play an important role in the clearance of amyloid β in the peripheral vascular system **[13].** High monocyte counts in the blood were observed in patients with AD **[14].**

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 **[15].** There is an inverse correlation between HDL-C, Tau protein, and amyloid β-42 protein **[16].** 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 induces vasorelaxation. HDL-C has an antioxidant effect to protect endothelial function **[17],[18]**.

In the pathophysiology of AD, inflammation plays an important role. Oxidative stress also plays a role in the early stages of AD. Reactive oxygen species increase in AD and result in membrane damage and cytoskeletal abnormalities in neural cells **[19]**. F2-isoprostanes, 3-nitrotyrosine, carbonylated proteins, and heme oxygenase type 1 are some markers of oxidative stress. Activated microglia secrete neurotoxin Aβ with some inflammatory molecules such as interleukin-1 (IL-1), interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-α), and interferon-gamma (IFNγ), and damage the neurons **[20]**.

MHR is known as an inflammatory and oxidative stress biomarker that is cost-effective and easily measurable **[21].** It can be measured easily and may be a cost-effective marker for the early diagnosis of AD.

When we examined the literature, we found no studies about MHR and AD. We planned to investigate whether there was a relationship between AD and MHR. The objective of this

study was to examine the differences in MHR between patients with AD and controls and 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 aged over 65 years 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 age and sex-matched patients with nonspecific symptoms such as dizziness and myalgia, who had normal cognitive functions, and had not been diagnosed as having dementia made up the control group **[22].** The age range of the AD group and control group was 68-93 years and 69-92 years, respectively. The patient group was divided into three groups according to the Clinical Dementia Grading (CDR) scale, mild, moderate, and severe. The global cognitive function of all subjects was evaluated using the Mini-Mental State Examination (MMSE) **[23].** A total score less than or equal to 24 was accepted as cognitive impairment. The control group subjects were older than 65 years and fully independent as regards 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 using a COBAS 8000 series (Switzerland) analyzer following 8 hours of overnight fasting. White blood cell measurements were performed using an

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-mimicking disorders; (4) Non-Alzheimer's dementia; (5) Rheumatologic 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 approved the study.

Statistical analysis: The IBM SPSS v23 software was used to analyze the study data. Normal distribution was determined using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Pearson's Chi-square test was used for evaluating categorical variables. Group pairwise comparisons were performed using 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 analyses and the Duncan test for normally distributed data and the Kruskal-Wallis H test and Dunn's test for non-normally distributed data, respectively. Risk factors that could affect AD were analyzed using a binary logistic regression model. Pearson's correlation coefficient and Spearman's rho correlation coefficient were used to analyze the relationship between normally and non-normally distributed quantitative data, respectively. Adjustment for confounding factors was performed using multivariate logistic regression models. The model was adjusted for age, sex, and the monocyte/HDL ratio; glucose, uric acid, triglyceride, and hemoglobin levels; and comorbidities. Statistical significance was set at $P<0.05$.

Results:

A total of 81 controls and 103 individuals diagnosed as having AD were included in the study. The sex distribution between the AD and control groups was similar **(*P*=0.478).** The groups showed no differences regarding sex and age (***P*=0.478 and *P*=0.688, respectively)**. Diabetes mellitus (DM) 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, but it was not statistically significant (***P*=0.64)** (**Table 1**). There was also a lack of statistically significant differences between the groups based on comorbidities (**Table 1**). The MHR value was found to be significantly higher in the AD group compared with the control group. 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's group when compared with the control group (**Table 2**).

The patients with AD 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 MMSE scores, which were significantly lower in the severe dementia subgroup **(*P*=0.001)**. Subgroup analysis was performed using the Kruskal-Wallis test. The MHR values of the moderate and severe AD subgroups were significantly higher than the control group **(*P*=0.012 and *P*=0.035, respectively).** Box plot graphs for each group are presented (**Figure 1**). The blood monocyte count was higher in the moderate severity dementia subgroup compared with 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 mean corpuscular hemoglobin concentration (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 did not affect AD development **(OR: 1.066, 95% 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. Also, a one-unit increase in the serum glucose level gave rise to a 1.008 times increase in AD risk. The risk factors analyzed in the regression model are presented in **Table 4**.

Discussion:

An increase in MHR was found in patients with AD 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.

We found no difference in MPV between the AD and control groups. Thrombocyte size is related to thrombocytosis in acute coronary syndrome or other vascular disorders. However, inflammation plays an important role in the basic pathology of AD.

MHR has also been investigated in patients with Parkinson's disease (PD). Although no difference was observed between patients with PD and a control group, MHR was higher in patients with PD with long-term follow-up **[24]**. Inflammation plays a role in the pathogenesis of α-synucleinopathy in PD. In the pathology of multiple system atrophy (MSA), there is systematic inflammation. It was shown that MHR was predominantly higher in MSA than in PD, which shows that MHR is a good marker for inflammatory conditions **[25].** MHR stands out as a marker reflecting inflammatory and oxidative stress in PD, similar to the neurodegenerative disorder AD, but is not a marker of early disease diagnosis because it is

higher in patients who are followed for a longer time. Although MHR was increased in the patients with AD compared with the control group in the current study, this was due to the larger number of patients with moderate and severe-stage disease than those with early-stage disease in the subgroup analysis.

Atherosclerosis or vascular problems may be encountered more commonly in patients with severe-stage AD. Hypertension may be a risk factor for cognitive impairment and AD in patients aged between 40 and 70 years who have a genetic predisposition to AD, especially those possessing APOE ε4 **[26]**. DM is also a risk factor for AD **[27]**. Hyperinsulinemia and brain insulin resistance in patients with DM stimulate amyloid β initiation in the brain. Also, hyperglycemia generates advanced glycation end products (AGEs) in DM. Increased AGEs trigger the production of receptors for AGEs (RAGEs). RAGEs lead to oxidative stress, vascular injury, and inflammation **[28]**.

The high MHR values in the late stages of AD demonstrate a potential for MHR to predict prognosis, as in coronary artery disease **[29]**,**[30]**. Changes in MHR may indicate an unfavorable prognosis related to vascular changes in AD. This cannot be mentioned as the main outcome of this study because of the absence of cardiovascular outcomes.

Various peripheral blood parameters have been studied in inflammatory disorders and also in AD **[31].** MPV was significantly increased in AD, and its value correlated with the severity of cognitive impairment **[32]**. A decreased hemoglobin level may be another blood parameter related to AD. It likely impacts cognitive function by decreasing cerebral blood perfusion, leading to neuroinflammation and oxidative stress **[33].** Despite this, we found no significant difference in hemoglobin levels between the groups. The reason for the difference in hemoglobin levels compared with the literature may be the role of the multifactorial pathophysiology in AD.

In some studies about MCV in AD, it was shown that MCV increased in AD compared with healthy controls **[34], [35]**. However, in a meta-analysis by Huang et al. (2022), it was mentioned that there was no significant difference in MCV between patients with AD and healthy controls **[36].** We found significant differences in terms of MCV between the groups, similar to Huang et al.'s results.

The limitations of this study include its retrospective design and the absence of data on factors such as smoking, alcohol consumption, cardiovascular data, body mass index, arterial blood pressure, and levels of inflammatory markers (e.g., IL-6, CRP, and TNF-α) of the patients. Neuropsychological tests (Letter Digit Substitution Task, Word Fluency Test, Stroop test, 15-word Verbal Learning Test, and Purdue Pegboard Test) were not been performed on the study population.

In conclusion, MHR negatively correlates with MMSE scores. MHR can be used as an index reflecting the increased AD risk but it cannot be used as a diagnostic test for AD. More extensive prospective studies about cardiovascular risk factors and inflammatory markers in AD with a larger scope are needed to demonstrate any such relationship more robustly.

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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 control group, 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 older than 65 years old from record of 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) (Figure 1). An increase in MHR was found in patients with AD.

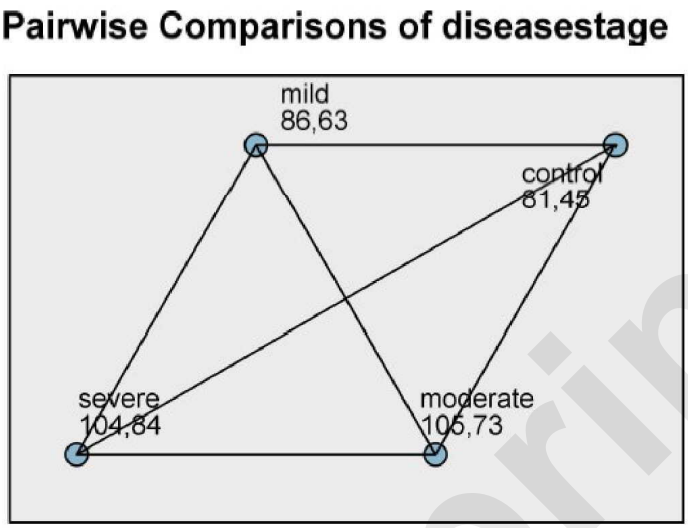

Figure 1: Pairwise comparisons of disease severity

Conclusion: High MHR values could not be used as a diagnostic test for AD.

Table I. 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 II. 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 III. Regression analysis of the quantitative data

		Age	MMSE	Monocytes	HDL-C	MHR	LDL-C	Cholesterol	Triglyceride	Glucose	MCV	MCHC	HGB
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**	0.719**
	p	**0.005**	**0.018**	0.184	0.709	0.480	**0.001**	**0.001**	0.181	0.405	**<0.001**	0.658	**<0.001**

*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: Hemoglobin, RBC: Red Blood Cell, MCHC: Mean Corpuscular Hemoglobin Concentration, MHR: Monocyte HDL-C Ratio

Table IV. 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

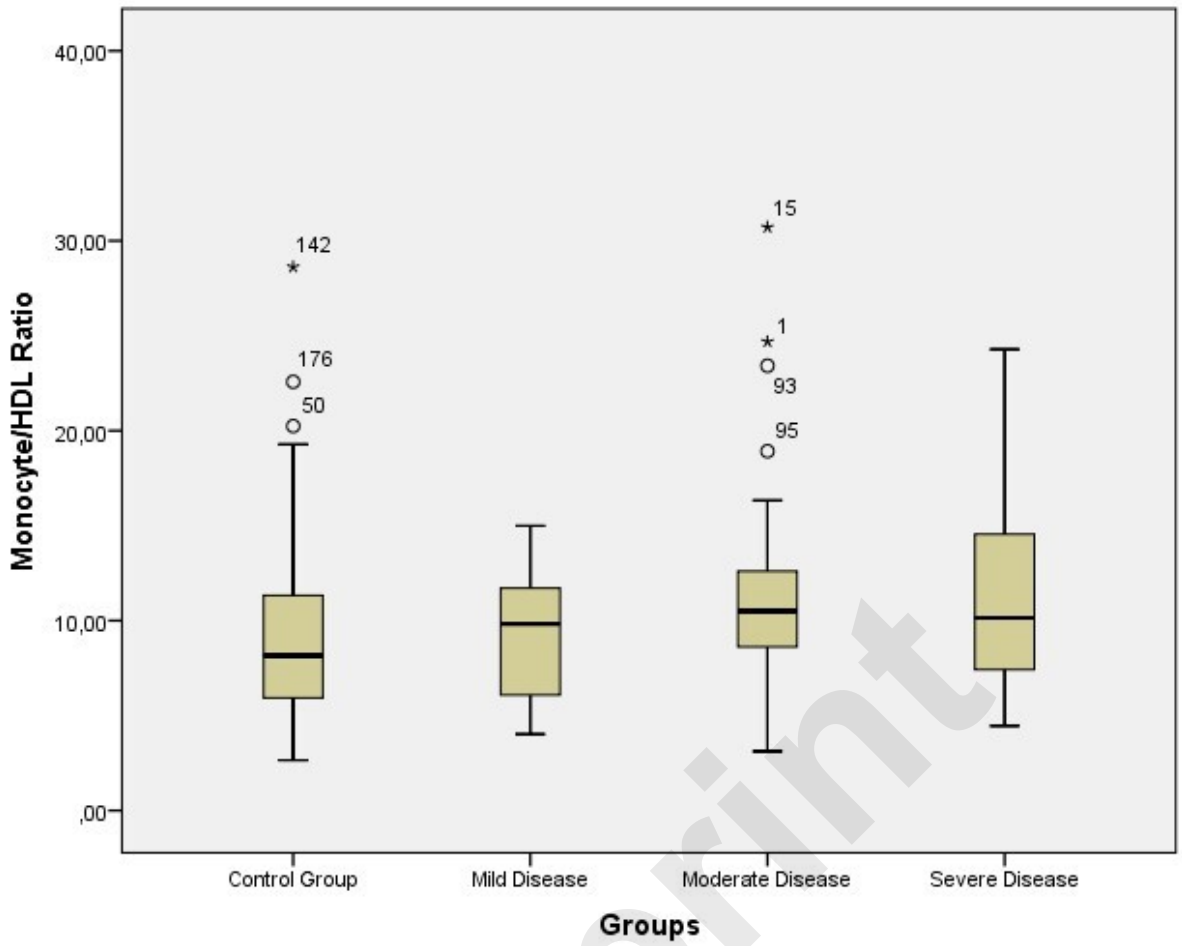

figure 1- pairwise comparisons of disease severity