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SELÇUK TIP DERGİSİ
SELCUK MEDICAL JOURNAL

DOI:http:/dx.doi.org/10.30733/std.2025.01771
Selcuk Med J 2025;41(1): 42-48

OPEN ARAŞTIRMA MAKALESİ / RESEARCH ARTICLE

Peripheral Biomarkers That May Be Associated with Mild Cognitive Impairment in Geriatric Patients

Geriatrik Hastalarda Hafif Bilişsel Bozuklukla İlişkili Olabilecek Periferik Biyobelirteçler

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ÖZET

Amaç: Hafif bilişsel bozukluk (HBB), bilişsel fonksiyonlarda azalmanın olduğu, erken müdahale edilmediği takdirde işlevsellikte kayıpların yaşandığı bir bozukluktur. Bu çalışmadaki amacımız HBB ile kontrol grubu arasında, nötrofil/yüksek- yoğunluklu lipoprotein kolesterol (HDLc) düzeyi oranı (NHO), monosit/HDLc oranı (MHO), ürik asit/HDLc oranı (UHO)'nı kıyaslamak ve bu parametrelerin HBB için prediktör bir biyobelirteç olarak kullanılıp kullanılamayacağını araştırmaktır.
Gereç ve Yöntemler: Kesitsel olan bu çalışmada 65 yaş üstü kişilerden ICD-10'a göre HBB tanısı konulan 68 kişi hasta grubunu oluşturdu. Kontrol grubu 65 yaş üzeri mental yeterlilik değerlendirmesi sonucu HBB olmayan bireylerden seçildi.
Bulgular: Monosit, UHO ve MHO seviyelerinin HBB grubunda daha yüksek olduğu görüldü (sırasıyla; p= 0.036, p= 0.007, p= 0.004). Mini-Mental Durum Muayene (MMSE) skoru ile HDLc seviyeleri arasında pozitif (p= 0.032), UHO arasında negatif yönlü ilişki (p= 0.019) bulundu. Tanı durumunu tahmin etmede UHO cut-off değeri= 0.1285 alındığında duyarlılığın %41.9 ve özgüllüğün %80.3 olduğu bulundu. MHO için cut-off değeri= 0.125 alındığında duyarlılığın %40.3 ve özgüllüğün %78.9 olduğu görüldü.
Sonuç: Düşük duyarlılık ve özgüllükte olsa da HBB tanısını tahmin etmede UHO ve MHO anlamlı bulundu. MMSE skoru ile HDLc seviyeleri arasındaki pozitif yönlü ilişki bulunması HDLc'nin bilişsel fonksiyonlara karşı koruyucu olabileceğini göstermektedir. UHO arttıkça MMSE skorunun düşmesi, UHO'nun prognozda kullanılabileceğine işaret edebilir. Çalışma sonuçlarımızın ileriye dönük çalışmalarla desteklenmesi gerekir.

Anahtar Kelimeler: Geriatri, mini-mental durum, bilişsel işlev, monosit/HDLc oranı, ürik asit/HDLc oranı

ABSTRACT

Aim: Mild cognitive impairment (MCI) is a disorder in which there is a decrease in cognitive functions and a loss of functionality is experienced unless early intervention is made. Our aim in this study was to compare neutrophil/high-density lipoprotein cholesterol (HDLc) levels ratio (NHR), monocyte/HDLc ratio (MHR), uric acid/HDLc ratio (UHR) between MCI and the control group and to investigate whether these parameters can be used as a predictive biomarker for MCI.
Materials and Methods: In this cross-sectional study, 68 people over the age of 65 who were diagnosed with MCI according to ICD-10 constituted the patient group. The control group was selected from individuals over the age of 65 who underwent the mental competence assessment and did not have MCI as a result of this assessment.
Results: Monocyte, UHR, and MHR were found to be higher in the MCI group (p= 0.036, p= 0.007, p= 0.004; respectively). A positive relationship was found between the Mini-Mental State Examination (MMSE) score and HDLc (p= 0.032) and a negative relationship was seen between UHR (p= 0.019). When the UHR cut-off value of 0.1285 was taken as a predictor of the diagnostic status, the sensitivity was found to be 41.9% and the specificity was 80.3%. When the cut-off value for MHR was taken as 0.125, the sensitivity was found to be 40.3% and the specificity was 78.9%.
Conclusion: Although they had low sensitivity and specificity, UHR and MHR were found to be significant in predicting the diagnosis of MCI. The positive relationship between the MMSE score and HDLc levels shows that HDLc may be protective against any deterioration in cognitive functions. The decrease in MMSE score while UHR increases may indicate that UHR can be used in prognosis. Our study results should be supported by prospective studies.

Keywords: Geriatrics, mini-mental state, cognitive function, monocyte/HDLc ratio, uric acid/HDLc ratio

Geliş Tarihi/Received: 17 July/Temmuz 2024 **Kabul Tarihi/Accepted:** 15 January/Ocak 2025 **Yayın Tarihi/Published Online:** 22 March/Mart 2025

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Atıf yapmak için/ Cite this article as: Imre O, Acat O, Karaagac M, Ekici F, Kocabas R. Peripheral Biomarkers That May Be Associated with Mild Cognitive Impairment in Geriatric Patients. Selcuk Med J 2025;41(1): 42-48

Disclosure: *Author has not a financial interest in any of the products, devices, or drugs mentioned in this article. The research was not sponsored by an outside organization. Author has agreed to allow full access to the primary data and to allow the journal to review the data if requested.*

INTRODUCTION

Mild Cognitive Impairment (MCI) is a disorder that lies somewhere between normal aging and Alzheimer's Disease (AD), characterized by more significant memory loss and neuronal loss compared to normal aging, making individuals more susceptible to AD (1). According to the World Health Organization, there are over 50 million people globally with dementia (2). The majority of these dementia cases are due to AD (3). In the elderly, there can be a natural mild decline in neurocognitive functionality with advancing age. These mild declines can rapidly progress to AD in some older adults. A study reported that 32% of MCI patients progressed to AD within two years (4). AD can reduce the quality of life and lead to accidents. Therefore, early diagnosis and treatment of MCI before it progresses to AD is crucial. Considering the pathophysiology of cognitive functions, a direct examination of the brain is necessary for a definitive diagnosis of cognitive impairment (5). This is quite costly and requires long waits, even until after death, for examination.

Cognitive impairment typically manifests itself in the later stages, leading to functional decline and the clinical presentation of AD, resulting in delays in diagnosing MCI (6). To detect cognitive function disorders early enough, various survey-based test batteries have been developed. Currently, AD diagnosis relies on clinical evaluation and neurocognitive tests like the Mini-Mental State Examination (MMSE) (7). In fact, the MMSE is not a direct diagnostic tool. Because it is closely related to the person's intellectual background, its diagnostic value is low. However, it can be used for screening. These questionnaire-based tests assess neurocognitive functions, including attention/working memory, executive-motor functions, processing speed, learning, and recollection. By their subjective nature, these tests have the potential for false positive and negative results. Therefore, MCI diagnosis is often supported with brain imaging (8). Given the expense and time-consuming nature of brain imaging, discovering simple, inexpensive, and quick peripheral biochemical parameters is important (9).

In the pathophysiology of AD, the increase in amyloid-beta (Aβ) in the brain parenchyma is known to play a role (10). Additionally, recent studies suggest that systemic and local mild chronic inflammation may contribute to the onset of neurodegeneration observed in AD (11). Individuals with elevated inflammatory markers have been found to have a higher risk of developing dementia (12, 13). Despite numerous studies, there is still no peripheral biochemical parameter with high validity and reliability that can predict, indicate prognosis, and definitively diagnose MCI.

The Neutrophil/High-Density Lipoprotein Cholesterol Ratio (NHR) is calculated by dividing the peripheral neutrophil count by the HDLc level. Similarly, the Monocyte/HDLc Ratio (MHR) is determined by dividing the monocyte count in peripheral blood by the HDLc level. NHR and MHR are emerging markers considered predictors of systemic inflammation and vascular diseases (14, 15). The close association of MCI with inflammation and vascular events suggests that these biomarkers could be related to MCI. Although the roles of NHR and MHR as new inflammatory markers have been investigated in various psychiatric disorders, there are no studies examining their relationship with MCI (16). The Uric Acid to High-Density Lipoprotein Cholesterol Ratio (UHR) has been studied in many chronic diseases potentially related to neurocognitive disorders in recent years, no literature exists yet on the association between UHR and MCI (17, 18).

The primary aim of this study is to compare levels of neutrophils, monocytes, uric acid, and HDLc, as well as the ratios of NHR, MHR, and UHR between patients diagnosed with the MCI and the control group. We seek to investigate whether these parameters can be used as biomarkers for the differential diagnosis of MCI. The secondary aim is to explore any potential correlation between MMSE scores and these biochemical parameters.

MATERIALS AND METHODS

In this cross-sectional study, the patient and control groups were selected from individuals over 65 years old who visited the outpatient psychiatry clinic at Karaman Training and Research Hospital between 2015 and 2023. The patient group included 68 individuals who met the MCI diagnosis criteria based on the clinical evaluation and MMSE results and were diagnosed with MCI according to ICD-10. The control group was selected from individuals who wanted to perform transactions at the notary or land registry office and were sent to the psychiatry polyclinic for a mental capacity report. In Turkey, people over the age of 65 are generally required to obtain a mental capacity report before they can perform transactions at the notary or land registry office. Individuals who applied for this report and had sufficient mental capacity designed the control group. Participants with chronic inflammatory diseases, those using anti-inflammatory drugs, those with hematological diseases, those in an acute infection period, those with a history of psychiatric disorders, and those using alcohol or narcotic substances were excluded from both the patient and control groups. The ones with hypertension and diabetes mellitus, common in this age group, were not excluded.

After obtaining the necessary permissions, the MMSE scores of the patients diagnosed with MCI were recorded from their hospital electronic records. The biochemical data from laboratory tests conducted at the time of their visit were also recorded. The control group was selected in reverse order from individuals over 65 years old, ensuring gender matching. Similarly, the MMSE values and biochemical data of the control group at that time were recorded. First, the biochemical data of the patient and control groups were compared. Secondly, the relationship between total MMSE scores and biochemical data was examined.

Ethics committee approval for the research was received from the Ethics Committee of Karamanoğlu Mehmetbey University from the Medical Faculty (Ethics Committee Decision No. 01-2024/2, dated 27.02.2024). This study was conducted in accordance with the guidelines stated in the principles of the Declaration of Helsinki.

Mini-Mental State Examination (MMSE)

The Mini-Mental State Examination (MMSE) was developed to evaluate cognitive function (19). In this study, the Turkish version of this test was used (20). The maximum score obtainable on this test is 30. It consists of five sections: 5 questions about time orientation, 5 questions on orientation to place, 3 on memory registration, 5 on attention and calculation, 3 on memory recall, 8 on language, and 1 on visual construction. The cut-off point for 'normal' cognitive function on the MMSE is 24. Any score of 23 or below indicates possible cognitive impairment. Scores between 19 and 23 are considered indicative of MCI. It has been reported that individuals scoring low on certain subscales of the MMSE have a higher risk of progressing to AD (21).

Statistical analysis

The SPSS 25.0 program was used to analyze the data. To ensure suitability of continuous variables to normal distribution, the normality test, q-q graph, skewness and kurtosis were taken into account. In these data, HDLc, uric acid, neutrophils, UHR, NHR showed normal distribution, while monocytes and MHR did not show normal distribution. Those with normal distribution were compared using the Independent T test, and those with non-normal distribution were compared through the Mann-Whitney U test. The Chi-square test was used to evaluate categorical data. Categorical data are reported as counts (n) and percentages (%), while continuous data are reported as means (M) and standard deviations (SD). Pearson Correlation test was used to evaluate the correlation. ROC analysis was used to estimate cut-off values for UHR and MHR. The AUC index value range is $0.5 \leq AUC \leq 1$. (For all analysis results, the cases in which the significance level was $p < 0.05$ were used.

RESULTS

The patient group was made up of 27.9% males (n= 19) and 72.1% females (n= 49), while the control group comprised 34.2% males (n= 26) and 65.8% females (n= 50). The mean age of the control group was 71.89±6.59, whereas that of the patient group was 68.76±5.74 (Table 1).

There was no significant difference between the groups in terms of HDLc levels, uric acid levels, neutrophil counts, and NHR values (p> 0.05). However, monocyte counts, UHR, and MHR values were found to be high in the patient group (p= 0.036, p= 0.007, p= 0.004; respectively), (Table 2).

A positive correlation was observed between MMSE score and HDLc levels (p= 0.032), while a negative correlation was found between MMSE score and UHR (p= 0.019), (Table 3).

In order to predict the diagnostic status, a cut-off value of

Table 1. Comparison of sociodemographic data in mild cognitive impairment and control groups

	Control (n=76)	MCI (n=68)	t/ χ^2	p
Age, Mean±SD	71.89±6.59	68.76±5.74	-3.02	0.003
Male, n(%)	26(34.2)	19(27.9)	0.657	0.418
Female, n(%)	50(65.8)	49(72.1)		
DM, n(%)	31(40.7)	26(38.2)	0.0979	0.754
HT, n(%)	34(44.7)	30(44.1)	0.0056	0.940

MCI: Mild cognitive impairment, DM: Diabetes mellitus, HT: Hypertension

Table 2. Comparison of biochemical parameters in mild cognitive impairment and control groups

	Control (n=76) Mean±SD	MCI (n=68) Mean± SD	t/Z	df	p
HDLc	52.44±12.20	48.42±14.53	-1.784	139	0.077
Uric acid	5.05±1.40	5.28±1.42	0.953	134	0.342
Neutrophil	4.69±1.55	4.53±1.92	-0.554	142	0.580
Monocyte	0.48±0.14	0.54±0.17	2061	142	0.036
UHR	0.10±0.04	0.12±0.06	2.752	132	0.007
MHR	0.009±0.0039	0.012±0.0059	1800	139	0.005
NHR	0.09±0.04	0.10±0.05	0.948	130	0.345

MCI: Mild cognitive impairment, HDLc: High density lipoprotein cholesterol, UHR: Uric acid/High density lipoprotein cholesterol ratio. MHR: Monocyte/High density lipoprotein cholesterol ratio, NHR: Neutrophil/High density lipoprotein cholesterol ratio. Data are presented as mean and standard deviation.

Table 3. MMSE Score Correlation Analysis with other variables

		HDLc	Uric acid	Neutrophil	Monocyte	UHR	MHR	NHR
MMSE Score	r	0.181*	-0.047	0.032	-0.105	-0.203*	-.194	-0.091

*: p< 0.05, Pearson Correlation Test was used.
MMSE: Mini-Mental State Examination Test, HDLc: High density lipoprotein cholesterol, UHR: Uric acid/High density lipoprotein cholesterol ratio, MHR: Monocyte/High density lipoprotein cholesterol ratio, NHR: Neutrophil/High density lipoprotein cholesterol ratio.

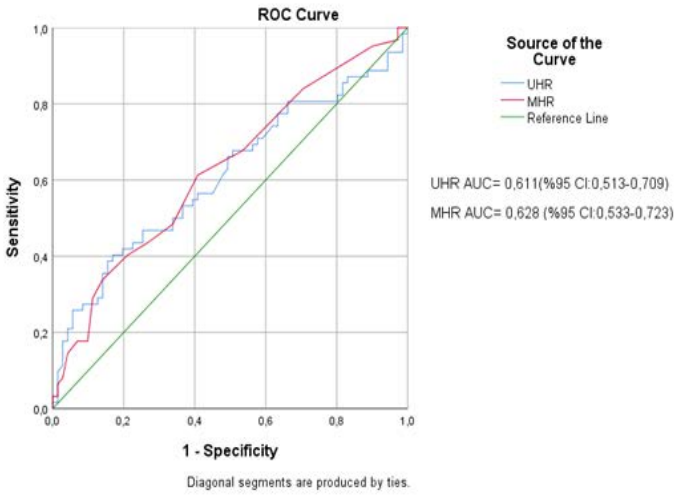

Figure 1. ROC Curve of UHR and MHR for Predicting Patients' Diagnosis

0.1285 was determined for UHR, with a sensitivity of 41.9% and a specificity of 80.3%. The area under the ROC curve was statistically significant at 0.611 (p= 0.027). For MHR, a cut-off value of 0.125 resulted in a sensitivity of 40.3% and a specificity of 78.9%. The area under the ROC curve was statistically significant at 0.628, (p= 0.011), (Figure 1).

DISCUSSION

In our study, when we compared the serum uric acid levels, neutrophil counts, monocyte counts and HDLc levels, UHR, MHR, and NHR rates of the MCI and control groups, it was seen that only monocyte counts, UHR and MHR were different between the two groups, and they were higher in the MCI group. UHR and MHR were found to be significant in predicting MCI diagnosis. MMSE was only associated with HDLc levels and UHR when correlated with biochemical parameters. There was a positive relationship between MMSE score and HDLc levels, and a negative relationship between MMSE score and UHR.

In our study, there was no significant difference in serum uric acid levels between the two groups. There are various studies on the relationship between uric acid and MCI. The results of these studies are conflicting. While some studies suggest that low uric acid levels are a risk factor for MCI (22), others have reported the opposite, indicating that high uric acid levels increase oxidation and lead to poor cognitive performance (23). A recent meta-analysis, similar to our study, concluded that there was no association between uric acid and cognitive impairment (24). These differences in the literature may be related to the stage of neurocognitive impairment. Uric acid can act as an antioxidant by inhibiting nitrite-mediated nitration, but it can also act as a pro-oxidant by generating radicals in reactions with various oxidants associated with inflammation (25, 26). Therefore, it seems that uric acid plays a dual role. Further prospective studies are needed to investigate the relationship between uric acid and cognition.

In this study, the monocyte count was found to be increased in the MCI group. There are few studies in the literature comparing monocyte counts between the MCI and control groups, with most studies focusing on the AD group. In a study, unlike our study, a significantly lower peripheral monocyte count was found in the AD group compared to the control group (27). Monocytes may reduce the development of AD by mediating the phagocytosis of amyloid-beta (Aβ) and tau, which play a role in AD pathophysiology (28). Therefore, a decrease in monocyte count may contribute to cognitive impairment by leading to the increase of amyloid-beta (Aβ) and tau. The difference in monocyte counts in studies may be related to the stage of neurocognitive impairment. The higher monocyte count found in our study may indicate a secondary increase for protective purposes against the disease (29). Further longitudinal studies evaluating monocytes in MCI patients who progress to AD are needed for definitive evidence.

In our study, unlike the data in the literature, no difference was found in terms of neutrophils between the two groups. Most studies in the literature on MCI report an increase in neutrophils (30), which has also been reported in AD patients. A meta-analysis reported increased neutrophil activation in MCI patients (31). According to another meta-analysis, neutrophils may have contributed to the progression of MCI patients to AD, suggesting that modulating neutrophils and their activities may be beneficial in preventing cognitive decline (32). Studies in the literature suggest that systemic inflammation may contribute to cognitive impairment by leading to neuroinflammation. Prospective follow-up of MCI patients and monitoring longitudinal changes in neutrophils would provide more accurate information for definitive evidence.

There is a wealth of data suggesting that HDLc levels have a positive effect on cognition. In a prospective study, it was reported that individuals with high HDLc levels in mid-life had a lower risk of developing MCI in old age after a 19-year follow-up, compared to those with low HDLc levels (33). However, in our study, no significant difference was found in serum HDLc levels between the MCI and control groups. The lack of difference between the two groups may be related to the early stage of MCI. Monitoring changes in serum HDLc levels in the same group of patients after MCI diagnosis as they age could provide more accurate information about the relationship between HDLc and cognitive function. The increase in MMSE scores with increasing HDLc levels in our study may suggest a protective effect of HDLc on cognitive function. Consistent with our findings, a study reported that MMSE scores showed a positive correlation with HDLc and a negative correlation with other lipid parameters in dementia patients (34). HDLc is believed to be protective against cognitive impairment by mediating antioxidant and anti-inflammatory systems (35). Large-scale prospective studies are needed for definitive evidence.

There was no significant difference between the MCI and control groups in terms of NHR values. A high NHR is indicative of an increase in neutrophils and a decrease in HDLc. There are no studies in the literature investigating NHR in the MCI patients. Most studies on NHR are related to cerebrovascular and cardiovascular diseases. This ratio reflects inflammatory activity and abnormal lipid metabolism, both of which impair vascular structure. A study indicated that NHR is associated with coronary artery stenosis and predicts the disease (36). An increase in this ratio has been reported to worsen the prognosis in cardiovascular diseases and may be a marker of mortality (37). Another study concluded that it may be associated with acute ischemic stroke (38). Considering the relationship between MCI and inflammatory events, cerebrovascular, and cardiovascular diseases, an elevation in NHR in MCI patients would be expected (39, 40). The lack of difference in NHR between the MCI and control in our study may be related to the early stage of the disease. Further studies with longitudinal follow-ups are needed to understand the relationship.

In our study, in comparison, MHR was found to be higher in the MCI group than in the control group. There are no studies in the literature investigating MHR in MCI patients. Most studies on MHR have been conducted in cerebrovascular and cardiovascular diseases. In these studies, a high MHR has been reported to predict the risk of stroke in ischemic patients and may be a marker of mortality in these patients (41). MHR has been found to negatively affect the course of cardiovascular diseases and be significantly associated with mortality (42). A high MHR is associated with an increase in monocyte count and a decrease in HDLc. It has been reported that HDLc may have an anti-inflammatory effect by inhibiting the expression of monocyte adhesion molecules such as CD11b and preventing the accumulation of monocytes in the vascular endothelium (43). A high MHR indicates that the balance between inflammatory and anti-inflammatory factors shifts towards inflammation in MCI patients. The fact that MHR can be a new inflammatory biomarker for cerebrovascular events and is closely related to prognosis in cardiovascular diseases suggests that it could be an important predictor for MCI patients.

In our study, UHR was found to be higher in the MCI group than in the control group. There are no studies in the literature investigating UHR in MCI patients. Most studies on UHR have been conducted in metabolic syndrome, diabetes, and thyroid patients, and UHR has been proposed as a new inflammatory marker (18, 44, 45). The inconsistent information between cognitive impairment and uric acid in the literature suggests that more consistent results could be obtained in MCI patients when uric acid is evaluated not alone but together with HDLc. The imbalance between the inflammatory effect of uric acid and the anti-inflammatory effect of HDLc may have impaired cognitive function.

Limitations

Our study has some limitations. Firstly, since our study is a cross-sectional study, we cannot know how these parameters will change as cognitive impairment progresses. Secondly, because hypertension and diabetes mellitus are commonly found in this age group, the effect of these diseases has not been excluded. Studies that exclude these limitations may provide more accurate results, as uncontrolled diabetes and hypertension can affect biochemical parameters. In our study, the proportion of those with hypertension and diabetes in the patient and control groups was equalized to reduce the effect of this limitation. Despite these limitations, our study may contribute to the literature as the first study to evaluate NHR, MHR, and UHR in MCI patients. It is expected that prospective, multicenter, and controlled studies will shed more light on this issue.

CONCLUSION

In this study, we found that monocyte count, UHR, and MHR were higher in the MCI patients compared to the control group. Although they have low sensitivity and specificity, UHR and MHR were found to be significant in predicting MCI diagnosis. The positive correlation between MMSE score and HDLc suggests that HDLc may be protective against impairment in cognitive functions. The decrease in MMSE score with increasing UHR may indicate the potential use of UHR in prognosis. Inflammation may play a role in the pathophysiology of MCI by affecting various pathways such as neurodegenerative processes, oxidative stress, and immune response. Therefore, more studies are needed that include more parameters of inflammation, oxidative stress, and immune response. Data from this study need to be supported by forthcoming prospective studies with the larger number of patients.

Conflict of interest: *The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.*

Financial conflict of interest: *Author declares that he did not receive any financial support in this study.*

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