BMC Geriatrics

RESEARCH Open Access

Could the monocyte-to-high-density lipoprotein cholesterol ratio serve as a reliable marker for orthostatic hypotension in older adults? A cross-sectional study

Suleyman Emre Kocyigit[1*] and Ali Kirik[2]

Abstract

Background Orthostatic Hypotension is a condition that increases in frequency with age and is associated with inflammation. This study investigates the relationship between the Monocyte-to-High-Density Lipoprotein Cholesterol Ratio (MHR) and OH in older adults.

Methods It was designed as a cross-sectional and observational study at our Geriatric outpatient clinic. Total of 229 patients were assessed retrospectively. OH was evaluated based on the active standing test. Logistic regression analysis was utilized to assess the association between MHR and both OH and supine hypertension (HT).

Results Of the 229 patients in the study, 73.5% were female, and the mean age was 76.75±6.52 years. The OH and control groups differed significantly in terms of sex, age, body mass index (BMI), malnutrition, frailty and probable sarcopenia. The MHRs were higher in both the OH group and the supine HT subgroup when compared to the control group ($p<0.05$). The cut-off value for MHR in the OH group was 9.28 ($p=0.023$). In a regression analysis, a significant relationship was observed between the presence of OH and MHR, independent of confounding factors (odds ratio (OR) 1.09;$p=0.045$). Similarly, an independent relationship was identified between the presence of supine HT and MHR (OR 1.1;$p=0.033$).

Conclusions MHR was found to be independently associated with OH in older adults, while supine HT within the OH group may be linked to MHR after adjusting for confounding factors.

Keywords Orthostatic hypotension, Supine hypertension, Monocyte-to-high-density lipoprotein cholesterol ratio, Geriatric syndromes, Aging

*Correspondence:
Suleyman Emre Kocyigit
suleymanemrekocyigit@gmail.com
[1]Department of Geriatric Medicine, Balikesir University Medicine of Faculty, Balikesir, Türkiye
[2]Department of Internal Medicine, Balikesir University Medicine of Faculty, Balikesir, Türkiye

Introduction

Orthostatic hypotension (OH) is a commonly observed, debilitating condition among people with such comorbid diseases as hypertension (HT) and diabetes mellitus (DM), as well as those suffering from neurodegenerative diseases [1], and serves also as a significant indicator of autonomic failure. OH is diagnosed based on a decrease of 20 mmHg or more in systolic blood pressure (SBP) and/or a decrease of 10 mmHg or more in diastolic blood pressure (DBP) during head-up tilt table or active standing tests within the initial three minutes of transitioning from a supine to a standing position [2]. Its prevalence in the general population averages around 6%, increasing with age, with a prevalence of around 28% in older adults [3, 4]. OH poses a risk for falls, syncope, fracture and cardiovascular disease, and increases the risk of mortality among older individuals [1].It is often asymptomatic and can often be overlooked in older adults. While baroreflex sensitivity failure stands as one of the primary mechanisms in its pathophysiology, atherosclerosis-related inflammatory processes also play a pivotal role in the development of OH [1, 5].

Monocytes – essential cells in the innate immune system – play a unique role in inflammatory processes, and a crucial role in the initial stage of atherosclerosis, binding to adhesion molecules expressed on damaged vascular endothelium through an immune-mediated process [6]. They also play a significant role in all stages of atherosclerosis [7]. HDL-C exerts anti-thrombotic, anti-oxidant, anti-inflammatory and anti-atherosclerotic effects, and elevated HDL-C levels, known for their anti-monocyte function, may confer protection against cardiovascular diseases [8]. The Monocyte-to-High-Density Lipoprotein Cholesterol Ratio (MHR) has recently emerged as a reliable marker for the prediction of inflammation and oxidative stress [9]. Studies have shown that MHR may be associated with stroke, coronary artery disease, atrial fibrillation, carotid intima-media thickness (CIMT) and the formation of carotid plaques [10]. Given the close relationship between these conditions and OH, there is an apparent need for a reliable and easily applicable marker for OH in older adults.

The relationship between OH, which is associated with atherosclerosis and inflammation, and MHR remains unknown in elderly adults, and our study seeks to alleviate this by investigating the potential relationship between OH and MHR in adults aged over 65 years, hypothesizing that MHR may exhibit a stronger association with those experiencing supine HT within the OH group.

Methods

Study design

For this retrospective, cross-sectional study, the hospital records of the 335 patients who attended our outpatient geriatric clinic between November 2022 and December 2023 were reviewed, and 229 with complete hospital records who gave their consent for participation and who did not meet the exclusion criteria were subsequently included in the study.

Inclusion criteria

The study included patients over the age of 65 years who presented to the geriatric clinic for any reason and who did not meet the exclusion criteria.

Exclusion criteria

Patients presenting with the following characteristics were excluded from the study: patients under 65 years of age, patients with anemia (those with HB levels < 10 g/dL), α-synucleopathies including Parkinson's, Lewy body dementia or multisystem atrophy causing OH, acute kidney injury or chronic kidney disease (estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m^2), history of acute cerebrovascular disease, aneurysm rupture, cavernous hemangioma, posttraumatic hemorrhage or hemorrhagic infarction, severe heart failure, severe valvular heart disease, carotid artery disease, atrial fibrillation, acute coronary syndrome or left bundle branch block, history of surgery within the last 3 months, dehydration, electrolyte imbalance, acute hemorrhage, sepsis, malignancy, paraneoplastic syndrome and similar serious co-morbidities, severe liver disease, use of lipid-lowering drugs, connective tissue diseases, inflammatory and infectious diseases.

Patient characteristics

Demographic features including age, sex, years of education, marital status, body mass index (BMI) and smoking history were retrieved from the patients' hospital records. Blood pressure was measured using an automatic oscillometric device (Friedrich Bosch Smart Digital Automated Blood Pressure Monitor), and hypertension (HT) was defined as systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg, or the use of any antihypertensive medication. Diagnoses of diabetes mellitus (DM) were based on American Diabetes Association criteria or the use of any anti-diabetic drug [11]. Recurrent falls were defined as falls occurring at least twice within the last year. Malnutrition was identified based on scores of 11 or below on the mini-nutritional assessment short form (MNA-SF) [12]. Probable sarcopenia was determined based on muscle strength assessed using a hand dynamometer, based on the European Working Group on Sarcopenia in Older People 2

(EWGSOP-2) criteria utilizing cut-off values established for the Turkish population (< 28 kg in men and < 14 kg in women) [13, 14]. Frailty was assessed based on the Fried Frailty Phenotype criteria, with a score of 3 or higher indicating frailty [15]. Polypharmacy was defined as the use of five or more medications. Diagnoses of dementia were based on the DSM-V diagnostic criteria [16].

Orthostatic hypotension

The active standing test was employed for the diagnosis of OH, being conducted in the morning following the administration of the patients' daily medications. The patients were advised to restrict caffeine intake and abstain from smoking, and to engage in 30 min of exercise before the test. Postural blood pressure was assessed using an automated oscillometric device, with the initial blood pressure measurement taken in the supine position and subsequent measurements taken within the third minute of standing. The patients were asked about any postural symptoms, such as dizziness and nausea, and OH was diagnosed based on a decrease of ≥ 20 mmHg in systolic blood pressure and ≥ 10 mmHg in diastolic blood pressure during the transition from the supine to standing position in the active standing test [2].

Laboratory findings

Blood samples were collected in the morning following a 12-hour fasting period, and subjected to a range of tests, including complete blood count with monocyte count, serum glucose, lipid profile, including total cholesterol, low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), triglycerides, C-reactive protein (CRP), estimated glomerular filtration rate (eGFR), serum albumin, serum electrolytes, folate, vitamin B12, ferritin and 25-hydroxy vitamin D levels. The monocyte-to-HDL-C ratio (MHR) was calculated using the formula: monocyte count ($x10^3$/L) divided by HDL-C (mg/dL). All biochemical analyses were performed using a Diagnostic Modular Systems autoanalyzer (Roche E170 and P-800).

Sample size

The sample size for the study was calculated using the G*Power program, which determined the requirement for a minimum of 190 participants, with an alpha value of 0.05 and a beta value of 0.80. The sample size of the study was thus deemed sufficient.

Statistical analysis

The patient groups were first divided into two groups: the OH group and the control group. Then, the OH group was divided into two groups: those with and without supine HT. Categorical variables are shown with a percentage (%). The Kolmogorov-Smirnov test was performed to ensure compliance with normal distribution for continuous variables. While normally-distributed variables are shown as mean+standard deviation, nonnormally-distributed variables are expressed as median[interquartile range]. Categorical data were compared with the Chi-square test. In comparing continuous data, if there were two groups, independent student t test was used for those with normal distribution and Mann-Whitney U test was used for those variables with a non-normal distribution. For the comparison of more than two groups, a one-way analysis of variance (ANOVA) was employed as a parametric test, while a Kruskal-Wallis test was used as the non-parametric test. Spearman's rank correlation coefficient was used to assess the association between MHR levels and other parameters. A Receiver Operating Characteristic (ROC) curve was generated to determine the cut-off values of MHR for predicting OH. Odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) for the independent association between MHR and the occurrence of OH were examined using a binary logistic regression analysis. MHR and the presence of supine HT or supine normotension within the OH group were compared to the non-OH group, analyzed based on multinomial logistic regression and adjusted for covariates. In both regression analyses, odds ratios (ORs) were calculated for three models: unadjusted, model 1 adjusted for age, gender, BMI, and model 2 adjusted for model 1 plus geriatric syndromes including malnutirition, frailty and sarcopenia. A p-value of less than 0.05 was considered statistically significant. All statistical analyses were conducted using IBM SPSS Statistics (Version 22.0. Armonk, NY: IBM Corp.).

Results

The mean age of the 229 patients in the present study was 76.75 ± 6.52 years, and 73.5% of the participants were female. The participants were initially divided into two groups: an OH group and a control group, with 98 patients in the OH group comprised. Comorbidities such as hypertension (HT) and diabetes mellitus (DM) were found to be similar between the two groups ($p > 0.05$). In a comparison of the demographic characteristics of the two groups, the age was found to be higher in the OH group ($p = 0.045$), the number of females and BMI levels were higher in the control group than in the OH group ($p < 0.05$). Among the geriatric syndromes, malnutrition, probable sarcopenia and frailty were significantly more prevalent in the OH group than in the control group ($p < 0.05$), LDL-C levels were lower in the OH group ($p = 0.027$), HDL-C levels were comparable between the two groups ($p > 0.05$), and both the monocyte count and MHR levels were higher in the OH group ($p < 0.05$) (Table 1). The OH group was subsequently subdivided into two subgroups based on the presence or absence of

Table 1 Comparison for demographic features, comorbities, geriatric syndromes, laboratory findings including MHR within all subjects and OH group

	OH (+) ***n*** **= 98**				**OH(-)** ***n*** **= 131**	***p*** **$_2$ value**
	All subjects ***n*** **= 98**	**Supine HT (+)** ***n*** **= 62**	**Supine HT (-)** ***n*** **= 36**	***p*** **$_1$ value**		
Demographic features						
Age (mean ± sd)	77.3 ± 5.9	78.5 ± 5.8	76.8 ± 5.9	0.073	75.6 ± 6.7	0.045
Gender (female;%)	65.3	64.8	66.7	0.079	78.6	0.025
Marital status (marriage;%)	49.0	54.9	33.3	0.150	44.3	0.377
Education year (med [IQR]	5[0]	5[0]	5[0]	0.500	5[0]	0.327
BMI (kg/m^2;mean ± sd)	25.7 ± 4.8	26.2 ± 4.9	24.7 ± 4.4	0.080	27.6 ± 5.3	0.044
Smoking history (%)	41.8	38.0	51.9	0.092	30.5	0.077
Comorbidities (%)						
Hypertension	71.4	71.8	70.4	0.898	74.0	0.659
Diabetes mellitus	36.7	36.6	37.0	0.968	35.1	0.800
Geriatric Syndromes (%)						
Recurrent falls	49.0	43.7	53.0	0.072	38.9	0.129
Urinary incontinence	62.2	66.2	57.1	0.410	60.3	0.766
Malnutrition	44.9	39.4	59.3	0.027	32.1	0.047
Frailty	48.0	40.8	66.7	0.006	33.6	0.028
Probable sarcopenia	54.1	52.1	59.3	0.061	38.9	0.023
Polypharmacy	65.3	66.0	74.1	0.436	61.1	0.511
Dementia	26.5	28.2	22.2	0.546	21.4	0.363
*Laboratory findings**						
Hemoglobin (g/dL)	12.3 ± 1.3	12.3 ± 1.2	12.4 ± 1.1	0.996	12.4 ± 1.4	0.974
Leucocyte (*10^3/μL)	7.1[3.4]	7.1[3.6]	6.8[2.6]	0.183	6.9[2.7]	0.084
Monocyte (*10^3/μL)	0.6[0.2]	0.6[0.3]	0.6[0.2]	0.036	0.5[0.2]	0.033
Glucose (mg/dL)	104[25.5]	106[23]	101[47.5]	0.338	108[37]	0.994
CRP (mg/L)	3[4.5]	3[4.7]	3[4.9]	0.142	3[2.7]	0.138
Total cholesterol (mg/dL)	210.0 ± 47.3	211.8 ± 52.5	205.2 ± 29.8	0.195	220.6 ± 45.8	0.090
Triglyceride (mg/dL)	140.5 ± 77.2	140.6 ± 79.8	140.3 ± 71.6	0.422	128.7 ± 58.1	0.189
HDL-C (mg/dL)	56.7 ± 15.8	55.9 ± 16.1	58.6 ± 14.9	0.684	57.0 ± 12.1	0.877
LDL-C (mg/dL)	127.0 ± 37.5	129.8 ± 40.6	119.5 ± 26.8	0.043	138.2 ± 38.4	0.027
MHR	10.6[8.9]	11.1[10.3]	10.2[4.1]	0.041	9.7[5.8]	0.023
eGFR (mL/min/1.73 m^2)	65.5 ± 17.4	65.9 ± 17.0	64.5 ± 18.8	0.610	67.9 ± 20.0	0.347
Albumin (g/dL)	4.0 ± 0.3	4.0 ± 0.2	4.0 ± 0.3	0.602	4.3 ± 0.7	0.314
Sodium (mmol/L)	139[3.5]	139[4]	137[5.2]	0.453	138[4]	0.980
Potassium (mmol/L)	4.3[0.7]	4.4[0.6]	4.1[0.8]	0.375	4.4[0.4]	0.078
Vitamin B12 (ng/L)	302[279.5]	287[309]	360.5[471]	0.167	256[285]	0.164
Folate (μg/L)	7.2[4.5]	8.1[5.2]	6.7[2.9]	0.293	7.4[3.9]	0.474
Ferritin (μg/L)	39.3[60.2]	38[58.6]	39.1[66.6]	0.621	30.2[50]	0.467
25-hydroxyvitamin d (μg/L)	19.4[16.9]	19[14.5]	22.7[18.7]	0.630	17.8[15.6]	0.660

CRP C-reactive protein, *eGFR* Estimated glomerular filtration rate, *HDL-C* High-density lipoprotein cholesterol, *IQR* Interquartile range, *med* Median, *LDL-C* low-density lipoprotein cholesterol, *MHR* Monocyte to high-density lipoprotein cholesterol ratio, *OH* Orthostatic hypotension, *sd* Standard deviation

*Normally-distributed variables is indicated with mean±SD. Not normally-distributed variables is shown as med [IQR]

p1: comparison for OH subgroups (supin hypertension and supin normotension) and control group

p2: comparison for OH group and control group

supine hypertension (HT), and the supine HT (+), supine HT (-) and control groups were compared. No significant differences were noted between the three groups in terms of demographic characteristics and comorbidities. MHR levels, and malnutrition and frailty frequencies were observed to be significantly different between the three groups ($p < 0.05$). After the application of the Bonferroni correction, it was determined that the MHR level was higher only in the supine HT group when compared to the control group ($p < 0.05$) (Table 1).

An analysis of the correlation between postural blood pressure changes and serum albumin, CRP and MHR

Table 2 Correlation between postural blood pressure changes and MHR, CRP and albumin level

	ΔSBP		ΔDBP	
	rho	*p* value	rho	*p* value
MHR	-0.141	0.033	-0.234	< 0.001
CRP (mg/L)	-0.086	0.330	-0.094	0.284
Albumin (g/dL)	0.114	0.091	0.086	0.186

CRP: C-reactive protein; DBP: diastolic blood pressure; MHR: monocyte to high-density lipoprotein cholesterol ratio; rho: correlation coefficient; SBP: systolic blood pressure

ΔSBP: Subtracting the systolic blood pressure in the supine position from the systolic blood pressure in the standing position

ΔDBP: Subtracting the diastolic blood pressure in the supine position from the diastolic blood pressure in the standing position

levels revealed that the changes in both SBP and DBP were correlated with MHR (rho: -0.141, $p = 0.033$ and rho: -0.234, $p < 0.05$, respectively), but not with serum albumin and CRP (Table 2).

In a ROC curve calculated to determine the MHR cut-off value for the presence of OH, the area under the curve (AUC) was measured as 0.588 ($p = 0.023$), while a cut-off value of 9.28 was identified for MHR in the OH group, with 60% sensitivity and 51% specificity (Fig. 1).

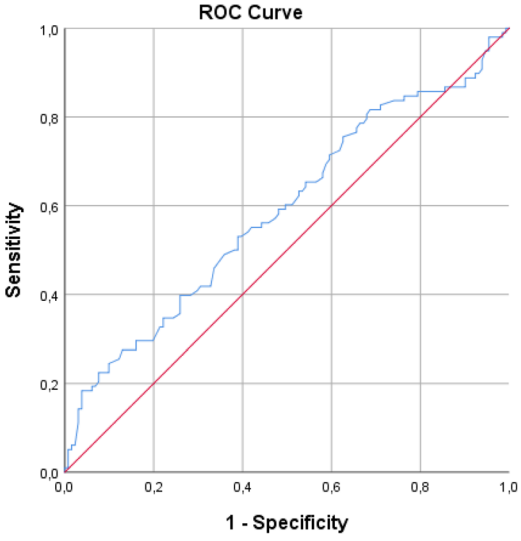
In a binomial regression analysis revealed between MHR and OH, the unadjusted odds ratio (OR) for MHR in the presence of OH was 1.08 (95% CI 1.02–1.14; $p = 0.007$). After the adjustment based on Model 1, the OR was determined as 1.11 (95% CI 1.01–1.21; $p = 0.019$), while adjustment based on Model 2 produced an OR of 1.09 (95% CI 1.00-1.20; $p = 0.045$). In a multinomial regression analysis examining the relationship between those with and without supine HT using the control group as the reference, no relationship was found in the supine HT (-) group, while a significant relationship was observed in the supine HT group in Model 2 (OR 1.1, 95% CI 1.01–1.22; $p = 0.033$) when compared to the control group (Table 3).

Discussion

This study has demonstrated that MHR values may be independently associated with OH, and further, that the supine HT identified in patients diagnosed with OH may be associated with MHR when adjusting for confounding factors.

OH stands out as a cardinal sign of cardiovascular autonomic dysfunction, and is particularly notable as a clinical finding, being indicative of sympathetic insufficiency [1]. Its frequency increases with age, with factors such as age-related physiological changes, elevated blood pressure, reduction in volume, medications that disrupt circulatory homeostasis, immobility, autonomic failure and increased frequencies of neurodegenerative diseases all having been linked to OH in older adults [17]. Although the reported prevalence of OH varies between studies, its frequency ranges from 12% to 60% in older adults admitted to hospitals as outpatients [18]. In the present study, the frequency of OH was found to be 40%, in line with the findings reported in literature.

OH represents a significant risk in older adults due to its potential to contribute to cardiovascular events,



AUC*	Sensitivity	Specificity	Cut-off of MHR	p value
0.588	0.60	0.51	9.28	0.023

AUC: area under rhe curve; MHR: : monocyte to high-density lipoprotein cholesterol ratio; rho:correlation coefficient; ROC: Receiver Operating Characteristic

Fig. 1 ROC curve showing cut-off value for MHR in patients with OH

Table 3 Logistic regression analysis of the relationship between the presence of MHR and the paitents with OH, supine hypertension in the OH subgroup

	Within all subjects* OH group vs. control group			Within OH group*					
				supine HT (+)			Supine HT (-)		
	OR	CI 95%	*p*value	OR	CI 95%	*p* value	OR	CI 95%	*p* value
Unadjusted	1.08	1.02–1.14	0.007	1.08	1.01–1.14	0.011	1.07	0.99–1.16	0.074
Mode1 1	1.11	1.01–1.21	0.019	1.11	1.01–1.22	0.024	1.09	0.97–1.22	0.121
Model 2	1.09	1.00-1.20	0.045	1.11	1.01–1.22	0.033	1.05	0.93–1.19	0.363

* reference category: control group

CI Confidence interval, *HT* Hypertension, *OH* Orthostatic hypotension, *OR* Odds ratio

Model 1: adjusted for age, gender, body mass index

Model 2: adjusted for Model 1 plus geriatric syndromes including malnutirition, frailty and sarcopenia

gait disorders, recurrent falls, impaired sleep quality, depression, stroke, renal failure, cognitive dysfunction and mortality [19–21]. Although OH is a common disorder in older adults, it is often overlooked due to its asymptomatic or atypical presentations. While multiple mechanisms contribute to its pathophysiology, the most significant include decreased baroreceptor reflex sensitivity, reduced alpha-1 adrenergic vasoconstrictor response to sympathetic stimulation, diminished parasympathetic activity, reduced water and salt retention in the kidney, atherosclerotic processes, decreased left ventricular diastolic filling and vascular inflammation [1, 22, 23]. Risk factors for OH include aging, diabetes mellitus (DM), hypertension (HT), carotid artery disease, stroke, vasoactive drug use, atrial fibrillation and renal failure [1]. It should be noted that all these risk factors can be associated with inflammation. For instance, inflammaging, characterized by the low-grade, chronic and systemic inflammation associated with aging, can contribute significantly to mortality and morbidity in older adults [24]. Inflammation also plays a pivotal role in other risk factors, particularly in such conditions as carotid artery disease [25]. In this regard, considering the association of these risk factors with OH, inflammation may play a significant pathophysiological role in the development of OH.

Monocytes are fundamental components of the innate immune system, regulating the secretion of inflammatory cytokines and participating in tissue remodeling, thereby contributing to chronic inflammation and cardiovascular events [26]. The activation of pattern recognition receptors in monocytes within the vascular wall is a crucial stage in the development of atherosclerosis [27]. Monocytes play a pivotal role in all stages of atherosclerosis, from the formation of foam cells to the eventual rupture of plaques [7]. Elevated monocyte levels are thus a primary determinant of adverse events in atherosclerotic diseases, which hold significant relevance in the pathophysiology of OH [27]. Epidemiological evidence has also demonstrated an association between monocyte count and both cardiovascular and all-cause mortality [28]. HDL-C prevents LDL oxidation in the vascular wall, hinders monocyte infiltration into vascular tissues, reduces monocyte activation through apoA1-mediated CD11b inhibition, suppresses monocyte proliferation and provides protection to endothelial cells, while also preventing the expression of monocyte tissue factors by inhibiting p38 activation and inositol phosphate kinase activity [10, 29, 30]. HDL-C also enhances endothelial function by upregulating the expression of endothelial nitric oxide synthase (NOS) and reducing the expression of adhesion molecules [31]. As a result of these factors, MHR has as a recently emerged as a marker in the context of inflammation and oxidative stress [32]. Previous studies have placed particular emphasis on the relationship between MHR and preclinical markers of atherosclerosis [7]. For example, there are studies reporting a relationship between MHR and various conditions, such as carotid intima-media thickness (CIMT), arterial stiffness in diabetic patients, carotid plaque formation and progression, cerebral small vessel diseases, ischemic stroke or transient ischemic attack, and atrial fibrillation [7, 10, 33–35]. While there are limited studies focusing on MHR in the over-65 age group, MHR has been demonstrated to be associated with peripheral artery disease and carotid plaques in older adults [27, 32]. MHR has been shown to have superior value than high-sensitivity CRP and fibrinogen-to-albumin ratio for the prediction of carotid artery stenosis – a condition that plays a pivotal role in the etiology of OH [6]. Similarly, in the present study, a positive correlation was identified between MHR and reductions in both systolic and diastolic blood pressure. Additionally, while MHR levels in the OH group differed significantly from those of the control group, no significant differences were observed in CRP and albumin levels. In other words, MHR may have greater predictive value for changes in orthostatic blood pressure than both CRP and albumin. Although the ROC analysis showed a statistically significant AUC (0.588), the discriminatory performance of MHR was modest, with limited sensitivity and specificity. Therefore, MHR should not be interpreted as a standalone diagnostic marker for OH. Rather, the

ROC analysis was performed for exploratory purposes to evaluate potential discriminatory capacity and to provide a preliminary threshold for future research. The main strength of our findings lies in the independent association observed in multivariable regression models, suggesting that MHR may reflect underlying inflammatory mechanisms contributing to OH rather than serving as a diagnostic tool.

There have been no studies to date analyzing the relationship between OH and MHR levels in older adults. In a population-based study OH is reported to increase the risk of myocardial infarction, stroke, heart failure and mortality [36]. Similar to MHR, it can be considered a reliable marker for predicting atherosclerosis, and there is also a need for reliable cardiovascular biomarkers for OH. Based on this premise, numerous proteomic markers have been investigated, among which, matrix metalloproteinase-7 (MMP-7) and T-cell immunoglobulin and mucin domain-1 (TIM-1) have been found to be independently associated with OH [36]. MMP-7 levels in particular may serve as a potential biomarker of cardiovascular disease risk in patients with OH given the known associations with atherosclerosis, coronary events and ischemic stroke [37]. In the present study elevated monocyte levels were noted in the OH group, while a further study reports that monocyte count and some monocyte subtypes play an independent role in predicting cardiovascular disease [38]. TIM-1 has been shown to be associated with carotid plaque formation, and contributes to atherosclerosis by affecting efferocytosis and the adaptive immune response [36, 39]. In particular, the monocyte subtype Ly6c + can have a direct impact on efferocytosis through toll-like receptors [40]. In this respect, it has been demonstrated that vascular inflammation plays a crucial role in the pathophysiology of OH, with monocytes potentially contributing to this process. There have also been studies directly investigating the significance of inflammatory biomarkers in OH, and the inflammatory pathway in OH may be a component of the underlying pathological processes that lead to autonomic failure [41]. The immune system is known to modulate autonomic activity, and inflammatory mediators in OH can serve as a crucial guide for diagnosis and treatment. The inflammatory biomarkers that are elevated in patients diagnosed with OH include immunoglobulin-like transcript 3 (ILT-3), midkine (MK), and regenerating islet-derived protein 4 (REG-4), among which, MK, in particular, facilitates endothelial cell proliferation, attracts inflammatory cells to the vascular wall, and contributes to plaque formation in atherosclerosis by inducing vascular stenosis and neointima formation [42, 43]. Similar to monocytes and MHR, MK also plays a vital role in atherosclerosis, with comparable effects. ILT-3 is an immunoregulatory protein that plays a crucial role in inducing immune tolerance, and is expressed in monocytes and antigen-presenting cells [42, 44]. This suggests that monocytes may directly participate in the pathophysiology of OH. REG-4 is associated with such risks as severe atherosclerosis, plaque stabilization, and coronary and cerebral vascular events [42]. In other words, monocyte count and MHR may have a significant direct or indirect effect on the pathophysiology of OH. In support of these findings, our study revealed both monocyte count and MHR to be associated with OH, independent of any confounding factors that may influence OH. Our study is the first to establish a relationship between OH and MHR in older adults. Although the observed odds ratios were numerically close to 1, it should be noted that MHR was analyzed as a continuous variable. The adjusted OR of 1.09 in Model 2 indicates a 9% increase in the odds of OH per one-unit increment in MHR. Considering the wide range of MHR values in our cohort, cumulative increases may translate into clinically relevant risk differences. Moreover, given the multifactorial nature of OH, large effect sizes would not be expected from a single inflammatory marker. Therefore, the association should be interpreted as modest but independent, reflecting a potential contribution of inflammatory burden to the pathophysiology of OH rather than a dominant causal determinant.

Supine HT is characterized by a paradoxical increase in blood pressure upon assuming a supine position for 5 to 10 min, and is associated with end-organ damage and cardiovascular outcomes in patients diagnosed with OH, and has also been demonstrated to be associated with cerebral oxygenation and cerebral autoregulation impairments [45]. In patients with alpha-synucleinopathy, increased white matter hyperintensity, decreased renal function and greater left ventricular hypertrophy are associated with earlier cardiovascular events and an increased risk of mortality [46]. The pathophysiology of supine HT remains poorly understood, although it is known to occur in the presence of increased systemic vascular resistance and excessive sympathetic tone in the supine position [47]. Supine HT is associated with arterial stiffness – a factor well-known to be related to MHR in diabetic patients [34, 45]. In the present study, a relationship with MHR in the supine HT subgroup was noted among patients with OH, regardless of confounding factors. It is plausible that inflammation may also contribute to supine HT, although further comprehensive studies are necessary to substantiate this hypothesis.

This study has several strengths, primarily, being the first study to reveal a relationship between OH and MHR in older adults. Secondly, it is the first study to suggest a relationship between supine HT and MHR, and thirdly, it identifies these findings as independent of covariates that may influence OH, including age. The present study also has several limitations, the first of which is

its retrospective and cross-sectional study design. Second, the head-up tilt table test was not used, which is more specific measurement of OH, although there have been past studies identifying the active standing test as a reliable and clinically easier alternative [48]. Third, the baroreflex sensitivity score was not calculated. Fourth, orthostatic blood pressure was assessed at a single visit, and repeated measurements were not performed. Given the variability of OH, this may have led to potential misclassification. Future studies with repeated orthostatic assessments would provide more robust diagnostic confirmation.

Conclusion

The present study demonstrates an independent association between MHR and OH in older adults. MHR should not be considered a substitute for orthostatic blood pressure testing; rather, it may serve as a complementary marker reflecting underlying inflammatory and vascular burden. Given the known cardiovascular risks associated with OH, MHR may provide additional insight into risk stratification in geriatric practice. However, prospective and longitudinal studies are required to determine its clinical utility and predictive value.

Acknowledgements
None.

Authors' contributions
Suleyman Emre KOCYIGIT: conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, writing – original draft, writing – review and editingAli KIRIK: conceptualization, data curation, investigation, methodology, project administration, resources, writing – original draft.

Funding
None.

Data availability
The author confrms that all data generated or analyzed during this study are included in this manuscript. The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The study was carried out in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the School of Medicine, Balikesir University in Balikesir, Türkiye (Ethic Committee Number: 2024/28). Informed consent was obtained from all participants.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 29 April 2025 / Accepted: 9 April 2026
Published online: 20 April 2026

References

1. Fedorowski A, Ricci F, Sutton R. Orthostatic hypotension and cardiovascular risk. Kardiol Pol. 2019;77(11):1020–7. https://doi.org/10.33963/KP.15055. PMID: 31713533.
2. Anonymous. Consensus statement on the definition of orthostatic hypotension, pure autonomic failure, and multiple system atrophy. The Consensus Committee of the American Autonomic Society and the American Academy of Neurology. Neurology. 1996. https://doi.org/10.1212/wnl.46.5.1470. 1996;46:1470. PMID: 8628505.
3. Ricci F, Manzoli L, Sutton R, et al. Hospital admissions for orthostatic hypotension and syncope in later life: insights from the Malmö Preventive Project. J Hypertens. 2017;35(4):776–83. https://doi.org/10.1097/HJH.0000000000001215. PMID: 28009704.
4. Räihä I, Luutonen S, Piha J, et al. Prevalence, predisposing factors, and prognostic importance of postural hypotension. Arch Intern Med. 1995;155(9):930–5. https://doi.org/10.1001/archinte.1995.00430090067008. PMID: 7726701.
5. Smith JJ, Porth CM, Erickson M. Hemodynamic response to the upright posture. J Clin Pharmacol. 1994;34(5):375–86. https://doi.org/10.1002/j.1552-4604.1994.tb04977.x. PMID: 8089249.
6. Yurtdaş M, Yaylali YT, Özdemir M. The role of monocyte to HDL ratio in predicting clinically significant carotid stenosis in patients with asymptomatic carotid artery disease. Rev Assoc Med Bras (1992). 2020;66(8):1043–1048. PMID: 32935796. https://doi.org/10.1590/1806-9282.66.8.1043.
7. Xi J, Men S, Nan J, Yang Q, Dong J. The blood monocyte to high density lipoprotein cholesterol ratio (MHR) is a possible marker of carotid artery plaque. Lipids Health Dis. 2022;21(1):130. PMID: 36463176. https://doi.org/10.1186/s12944-022-01753-4.
8. Ganjali S, Momtazi AA, Banach M, et al. HDL abnormalities in familial hypercholesterolemia: Focus on biological functions. Prog Lipid Res. 2017;67:16–26. https://doi.org/10.1016/j.plipres.2017.05.001. PMID: 28506805.
9. Canpolat U, Çetin EH, Cetin S, et al. Association of Monocyte-to-HDL Cholesterol Ratio with Slow Coronary Flow is Linked to Systemic Inflammation. Clin Appl Thromb Hemos. 2016;22(5):476–82. https://doi.org/10.1177/1076029615594002. PMID: 26139836.
10. Zhang Z, Gao Y, Li Z et al. Association of carotid atherosclerotic plaque and intima-media thickness with the monocyte to high-density lipoprotein cholesterol ratio among low-income residents of rural China: a population-based cross-sectional study. BMC Public Health. 2023;23(1):2541. PMID: 38115018. https://doi.org/10.1186/s12889-023-17447-0.
11. American Diabetes Association. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2019. Diabetes Care. 2019;42(Suppl 1):S13–28. https://doi.org/10.2337/dc19-S002. PMID: 30559228.
12. Guigoz Y. The Mini Nutritional Assessment (MNA) review of the literature–What does it tell us? J Nutr Health Aging. 2006;10(6):466–87. PMID: 17183419.
13. Cruz-Jentoft AJ, Bahat G, Bauer J, et al. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing. 2019;48(1):16–31. https://doi.org/10.1093/ageing/afz046. PMID: 30312372.
14. Ates Bulut E, Soysal P, Dokuzlar O, et al. Validation of population-based cutoffs for low muscle mass and strength in a population of Turkish elderly adults. Aging Clin Exp Res. 2020;32(9):1749–55. https://doi.org/10.1007/s40520-019-01448-4. PMID: 31898170.
15. Fried LP, Tangen CM, Walston J, Cardiovascular Health Study Collaborative Research Group. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001;56(3):M146-56. PMID: 11253156. https://doi.org/10.1093/gerona/56.3.m146.
16. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. Fifth Edition Arlington, VA: American Psychiatric Association; 2013.
17. Luukinen H, Koski K, Laippala P, Kivelä SL. Prognosis of diastolic and systolic orthostatic hypotension in older persons. Arch Intern Med. 1999;159(3):273–80. https://doi.org/10.1001/archinte.159.3.273. PMID: 9989539.
18. Mol A, Bui Hoang PTS, Sharmin S et al. Orthostatic Hypotension and Falls in Older Adults: A Systematic Review and Meta-analysis. J Am Med Dir Assoc. 2019;20(5):589–597.e5. PMID: 30583909. https://doi.org/10.1016/j.jamda.2018.11.003.
19. Rockwood MR, Howlett SE, Rockwood K. Orthostatic hypotension (OH) and mortality in relation to age, blood pressure and frailty. Arch Gerontol Geriatr. 2012;54(3):e255-e260. PMID: 22240412. https://doi.org/10.1016/j.archger.2011.12.009.
20. Perlmuter LC, Sarda G, Casavant V, et al. A review of orthostatic blood pressure regulation and its association with mood and cognition. Clin Auton

Res. 2012;22(2):99–107. https://doi.org/10.1007/s10286-011-0145-3. PMID: 21948454.
21. Soysal P, Yay A, Isik AT. Does vitamin D deficiency increase orthostatic hypotension risk in the elderly patients? Arch Gerontol Geriatr. 2014;59(1):74–7. https://doi.org/10.1016/j.archger.2014.03.008. PMID: 24742775.
22. Huang JJ, Sharda N, Riaz IB, Alpert JS. Summer syncope syndrome. Am J Med. 2014;127(8):787–90. https://doi.org/10.1016/j.amjmed.2014.02.037. PMID: 24613712.
23. Gupta V, Lipsitz LA. Orthostatic hypotension in the elderly: diagnosis and treatment. Am J Med. 2007;120(10):841–7. https://doi.org/10.1016/j.amjmed.2007.02.023. PMID: 17904451.
24. Franceschi C, Campisi J. Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases. J Gerontol A Biol Sci Med Sci. 2014;69 Suppl 1:S4. PMID: 24833586. https://doi.org/10.1093/gerona/glu057.
25. Goikuria H, Vandenbroeck K, Alloza I. Inflammation in human carotid atheroma plaques. Cytokine Growth Factor Rev. 2018;39:62–70. https://doi.org/10.1016/j.cytogfr.2018.01.006. PMID: 29396056.
26. Bilik MZ, Oylumlu M, Oylumlu M, et al. Novel predictor of pulmonary arterial hypertension: Monocyte to HDL cholesterol ratio. Med (Baltim). 2022;101(34):e29973. https://doi.org/10.1097/MD.0000000000029973. PMID: 36042653.
27. Selvaggio S, Abate A, Brugaletta G, et al. Platelet-to-lymphocyte ratio, neutrophil-to-lymphocyte ratio and monocyte-to-HDL cholesterol ratio as markers of peripheral artery disease in elderly patients. Int J Mol Med. 2020;46(3):1210–6. https://doi.org/10.3892/ijmm.2020.4644. PMID: 32705268.
28. Jiang M, Yang J, Zou H et al. Monocyte-to-high-density lipoprotein-cholesterol ratio (MHR) and the risk of all-cause and cardiovascular mortality: a nationwide cohort study in the United States. Lipids Health Dis. 2022;21(1):30. PMID: 35300686. https://doi.org/10.1186/s12944-022-01638-6.
29. Soran H, Hama S, Yadav R, Durrington PN. HDL functionality. Curr Opin Lipidol. 2012;23(4):353–66. https://doi.org/10.1097/MOL.0b013e328355ca25. PMID: 22732521.
30. Murphy AJ, Woollard KJ, Hoang A et al. High-density lipoprotein reduces the human monocyte inflammatory response. Arterioscler Thromb Vasc Biol. 2008;28(11):2071-7. PMID: 18617650. https://doi.org/10.1161/ATVBAHA.108.168690.
31. Zhang H, Lu J, Gao J et al. Association of Monocyte-to-HDL Cholesterol Ratio with Endothelial Dysfunction in Patients with Type 2 Diabetes. J Diabetes Res. 2024;2024:5287580. PMID: 38239233. https://doi.org/10.1155/2024/5287580.
32. Zhao S, Tang J, Yu S, et al. Monocyte to high-density lipoprotein ratio presents a linear association with atherosclerosis and nonlinear association with arteriosclerosis in elderly Chinese population: The Northern Shanghai Study. Nutr Metab Cardiovasc Dis. 2023;33(3):577–83. https://doi.org/10.1016/j.numecd.2022.12.002. PMID: 36646605.
33. Xu Q, Wu Q, Chen L, et al. Monocyte to high-density lipoprotein ratio predicts clinical outcomes after acute ischemic stroke or transient ischemic attack. CNS Neurosci Ther. 2023;29(7):1953–64. https://doi.org/10.1111/cns.14152. PMID: 36914580.
34. Mayasari DS, Taufiq N, Hariawan H. Association of monocyte-to-high density lipoprotein ratio with arterial stiffness in patients with diabetes. BMC Cardiovasc Disord. 2021;21(1):362. PMID: 34330221. https://doi.org/10.1186/s12872-021-02180-6.
35. Nam KW, Kwon HM, Jeong HY, Park JH, Min K. Monocyte to high-density lipoprotein cholesterol ratio is associated with cerebral small vessel diseases. BMC Neurol. 2024;24(1):18. PMID: 38178033. https://doi.org/10.1186/s12883-023-03524-9.
36. Johansson M, Ricci F, Aung N, et al. Proteomic Profiling for Cardiovascular Biomarker Discovery in Orthostatic Hypotension. Hypertension. 2018;71(3):465–72. https://doi.org/10.1161/HYPERTENSIONAHA.117.10365. PMID: 29295851.
37. Abbas A, Aukrust P, Russell D, et al. Matrix metalloproteinase 7 is associated with symptomatic lesions and adverse events in patients with carotid atherosclerosis. PLoS ONE. 2014;9(1):e84935. https://doi.org/10.1371/journal.pone.0084935. PMID: 24400123.
38. Chen JW, Li C, Liu ZH et al. The Role of Monocyte to High-Density Lipoprotein Cholesterol Ratio in Prediction of Carotid Intima-Media Thickness in Patients with Type 2 Diabetes. Front Endocrinol (Lausanne). 2019;10:191. PMID: 31019490. https://doi.org/10.3389/fendo.2019.00191.
39. Lind L, Ärnlöv J, Lindahl B, et al. Use of a proximity extension assay proteomics chip to discover new biomarkers for human atherosclerosis. Atherosclerosis. 2015;242(1):205–10. https://doi.org/10.1016/j.atherosclerosis.2015.07.023. PMID: 26204497.
40. Larson SR, Atif SM, Gibbings SL, et al. Ly6C(+) monocyte efferocytosis and cross-presentation of cell-associated antigens. Cell Death Differ. 2016;23(6):997–1003. https://doi.org/10.1038/cdd.2016.24. PMID: 26990659.
41. Peçanha T, Lima AH. Inflammation and cardiovascular autonomic dysfunction in rheumatoid arthritis: a bidirectional pathway leading to cardiovascular disease. J Physiol. 2017;595(4):1025–6. https://doi.org/10.1113/JP273649. PMID: 28198018.
42. Johansson M, Ricci F, Aung N, et al. Inflammatory biomarker profiling in classical orthostatic hypotension: Insights from the SYSTEMA cohort. Int J Cardiol. 2018;259:192–7. https://doi.org/10.1016/j.ijcard.2017.12.020. PMID: 29579600.
43. Horiba M, Kadomatsu K, Yasui K, et al. Midkine plays a protective role against cardiac ischemia/reperfusion injury through a reduction of apoptotic reaction. Circulation. 2006;114(16):1713–20. https://doi.org/10.1161/CIRCULATIONAHA.106.632273. PMID: 17015789.
44. Jensen MA, Yanowitch RN, Reder AT, White DM, Arnason BG. Immunoglobulin-like transcript 3, an inhibitor of T cell activation, is reduced on blood monocytes during multiple sclerosis relapses and is induced by interferon beta-1b. Mult Scler. 2010;16(1):30–8. https://doi.org/10.1177/1352458509352794. PMID: 20007427.
45. Newman L, O'Connor JD, Romero-Ortuno R, Reilly RB, Kenny RA. Supine Hypertension Is Associated With an Impaired Cerebral Oxygenation Response to Orthostasis: Finding From The Irish Longitudinal Study on Ageing. Hypertension. 2021;78(1):210–9. https://doi.org/10.1161/HYPERTENSIONAHA.121.17111. PMID: 34058851.
46. Palma JA, Redel-Traub G, Porciuncula A, et al. The impact of supine hypertension on target organ damage and survival in patients with synucleinopathies and neurogenic orthostatic hypotension. Parkinsonism Relat Disord. 2020;75:97–104. https://doi.org/10.1016/j.parkreldis.2020.04.011. PMID: 32516630.
47. Jordan J, Biaggioni I. Diagnosis and treatment of supine hypertension in autonomic failure patients with orthostatic hypotension. J Clin Hypertens (Greenwich). 2002;4(2):139–45. https://doi.org/10.1111/j.1524-6175.2001.00516.x. PMID: 11927799.
48. Finucane C, van Wijnen VK, Fan CW, et al. A practical guide to active stand testing and analysis using continuous beat-to-beat non-invasive blood pressure monitoring. Clin Auton Res. 2019;29(4):427–41. https://doi.org/10.1007/s10286-019-00606-y. PMID: 31076939.

Publisher's note