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CLINICAL STUDY

Systemic inflammatory response index and monocyte-to-high density lipoprotein ratio- new biomarkers remarking the inflammation in primary sarcopenia: The SIMPS study

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ABSTRACT

OBJECTIVE: To investigate the relationship of sarcopenia with systemic inflammation response index (SIRI), monocyte to high-density lipoprotein ratio (MHR) and platelet parameters in geriatric patients.

METHODS: We designed a cross-sectional retrospective study in patients presented to a geriatric outpatient clinic for the first time. The diagnosis of sarcopenia was made in accordance with the EWGSOP2 criteria. SIRI, MHR, mean platelet volume /Platelet count (MPV/Plt), platelet distribution width /Platelet (PDW/Plt), platelet/lymphocyte ratio (PLR) were calculated from fasting blood test results at the time of admission.

RESULTS: Among 262 patients, 79 patients (30.1%) with sarcopenia had significantly higher frequencies of delirium, hypothyroidism, chronic kidney disease and probable depression (p=0.010; p=0.018; p=0.034; p<0.001). Malnutrition scores and cognitive impairment scores were significantly lower in sarcopenic group (p<0.001 for both). Patients with sarcopenia had significantly higher MHR, SIRI and C-reactive protein values than patients without sarcopenia (p<0.001; p=0.001 and p=0.006, respectively). No significant difference was found between the groups in terms of MPV/Plt, PDW/Plt, PLR (p=0.605; p=0.920; p=0.510). Area under the curve for MHR was 0.675 (95% CI: 0.604-0.746, p<0.001) and 0.601 (95% CI: 0.523–0.679, p=0.010) for SIRI. A sensitivity of 72.2% and a specificity of 55.7% were found for MHR>0.99.

CONCLUSIONS: The finding of higher MHR and SIRI in geriatric sarcopenia patients supports low-grade chronic inflammation in the pathophysiology of sarcopenia. These non-invasive, cost-effective and simple parameters based on traditional peripheral blood cell counts may be warning signs for sarcopenia in the geriatric population *(Tab. 3, Fig. 1, Ref. 25)*. Text in PDF *www.elis.sk*

KEY WORDS: primary sarcopenia, inflammation, systemic inflammation response index, monocyte/high-density lipoprotein ratio, platelet parameters.

Introduction

Sarcopenia is one of the most striking issues in geriatrics because of the many adverse clinical outcomes and mortality. Sarcopenia is closely associated with frailty, falls, suppression of the immune system and increases the risk of hospitalization, length of stay, health care costs, morbidity and mortality (1, 2). Studies have shown that both muscle strength and muscle mass decrease with advancing age (3). According to the European Working Group on Sarcopenia in Older People (EWGSOP2) definition, the presence of low muscle strength is 'possible sarcopenia' and the presence of low muscle mass in addition to low muscle strength is called 'sarcopenia' (4). Age-related sarcopenia without any other underlying cause is defined as primary sarcopenia. Although the pathogenesis of sarcopenia is still unclear, chronic low-grade inflammation is believed to play an important role in this process (5, 6).

Some platelet parameters have been suggested to represent inflammation. However, since these values can be affected by various conditions and diseases such as diabetes mellitus, hypertension, cancer, hypercholesterolaemia, smoking and obesity, there are different results in the literature in their use as indicators of inflammation (7, 8). The systemic inflammation response index (SIRI), an indicative of chronic low-grade inflammation, reflects the balance of host immunity and inflammation. Likewise, monocyte to high-density lipoprotein ratio (MHR) shows the balance of inflammation, anti-inflammation and antioxidation (9, 10).

The relationship between these novel inflammatory parameters and many inflammatory diseases has been clearly demonstrated in studies, but their relationship with primary sarcopenia, which can be difficult to diagnose, has not been investigated before. Therefore, we aimed to contribute to the literature by investigating the relationship between sarcopenia and platelet indices, SIRI and MHR.

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Methods

Study design and participants

We designed a cross-sectional retrospective study. A total of 262 participants aged 65 and over who applied to the geriatric outpatient clinic of a university hospital were included. Ethical approval was obtained from the ethics committee of Cerrahpaşa Medical Faculty (02.05.2023–679433) that conforms to the provisions of the Declaration of Helsinki (as revised in Tokyo in 2004).

Comprehensive geriatric assessment

Nutritional status was evaluated with the Mini Nutritional Assessment (MNA) long form, and patients with a score of less than 23.5 out of 30 points were considered to be at risk of malnutrition and malnourished (11). Mini-mental state examination (MMSE) scale was used to determine cognitive impairment. A score below 24 in the test, which was evaluated over 30 points, was accepted as a decrease in cognitive functions (12). Presence of depression possibility was evaluated with the short form of the geriatric depression scale (GDS), and 5 or more was considered as possible depression (13). The risk of falls was evaluated with the mobility assessment test and a low score indicates a high risk of falls. Katz BADL (basic activities of daily life) and Lawton-Brody IADL (instrumental activities of daily life) scales were used to assess the independence of study participants. The Katz BADL scale is scored between 0 and 27, and as the score increases, the patient's dependence increases (14). On the Lawton-Brody IADL scale, patients are given a score between 0 and 17, and as the score decreases, the patient's dependence increases (15).

Data collection

In clinical practice, handgrip and bioelectrical impedance analysis (BIA) measurements are routinely performed for each patient at the first admission to our geriatrics outpatient clinic. Clinical information, baseline patient characteristics, including demographics, comprehensive geriatric assessment (CGA) scores, muscle measurements and bioelectrical impedance analysis (BIA) measurement were retrived from patients files and routine fasting blood test results at the time of admission were obtained from the electronic hospital data system.

The calculations for MPV/Plt, PDW/Plt, PLR, SIRI and MHR were as follows: MPV/Plt= Mean platelet volume to platelet count ratio; PDW/Plt= Platelet distribution width to platelet count ratio; PLR = platelet count to lymphocyte count ratio; SIRI = neutrophil count × monocyte count/lymphocyte count; and MHR = monocyte count/high-density lipoprotein.

Assessment of sarcopenia

EWGSOP2 diagnostic criteria were used in the evaluation of sarcopenia, and patients with both low muscle strength and muscle mass were diagnosed as sarcopenia (4). A hand dynamometer (Takei TKK 5401 model, Takei Scientific Instruments Co., Tokyo, Japan) was used to measure skeletal muscle strength. Three measurements were performed for both hands with 10-second intervals between each measurement and the greatest value was recorded. Cut-off value for the handgrip test was considered 27 kg for men and 16 kg for women. BIA device (Tanita Body Composition Analyzer® TBF-300 model, Tanita Co., Tokyo, Japan) was used to evaluate skeletal muscle mass. Skeletal muscle mass index (SMMI) was calculated with SMM/height^2 (kg/m^2) formula. As specified in EWGSOP2, SMMI cut-off value was considered as 7.0 kg/m^2 for men and 5.5 kg/m^2 for women. Gait speed was considered normal when the test result was ≥0.8 m/s.

We had some exclusion criteria when forming our study population. Patients under 65 years of age, with a clinical diagnosis of malignancy, having an active infection, terminal illness, chronic systemic inflammatory disorders and hematological diseases affecting the results of complete blood count, amputated extremity and metalic device that interfered with muscle mass assessment and patients with missing data were excluded from the study. Only the data of the patients who were able to cooperate with the tests and completed the measurements were included. Using the above exclusion criteria, 282 patients who were eligible for the study were re-evaluated with blood test results. 5 patients with CRP>20 mg/L, 5 patients with erythrocyte sedimentation rate >50 mm/hr, 1 patient with white blood cells>15x10^3/μL, 7 patients with neutrophils >10x10^3/μL, and 2 patients with lymphocytes >6x10^3/μL were not included in the study.

Statistical analysis

Categorical variables were expressed as numbers and percentages. A chi-square test or Fisher's exact test was used to compare categorical variables. Continuous variables were presented as mean±standard deviation. Student's t-test was used for continuous variables. The multivariate logistic regression (LR) was applied for the parameters that were significantly different between the two groups. Multivariate associations were reported as odds ratio (OR) with 95% confidence interval (CI). Receiver operating characteristic (ROC) curve analysis was performed for MHR and SIRI for the diagnostic accuracy of sarcopenia. The area under the curve (AUC) was then estimated with a 95% confidence interval (CI). p value <0.05 was considered statistically significant. Data were analyzed by Statistical Package for Social Sciences (SPSS for Windows, v21.0; IBM Corp. Armonk, NY, USA).

Results

Of the 262 patients included in our study, 79 (30.1%) had sarcopenia. 53 (67%) of the patients with sarcopenia and 133 (72.6%) of the patients without sarcopenia were female. The mean age of the patients with sarcopenia (79.59±7.19) was statistically significantly higher than the mean age of the patients without sarcopenia (75.24±6.91) (p<0.001). The most common comorbid diseases in the study population were hypertension (74%), diabetes mellitus (48.8%) and osteoporosis (30.2%), respectively. In patients with sarcopenia, the frequency of delirium, hypothyroidism and chronic kidney disease was statistically significantly higher than in patients without sarcopenia (p=0.010; p=0.018; p=0.034; respectively).

When the two groups were compared in terms of CGA tests, SMMT, MNA and mobility scores were significantly lower (p<0.001, for all) and GDS was significantly higher (p<0.001) in the sarcopenia group. Comparing ADLs and IADLs, sarcopenic patients were found to be more dependent (p=0.001; p=0.14). As expected, the hand grip strength and calf circumference of the patients in the sarcopenia group were lower (p<0.001; p=0.026), and their walking speed was slower (p<0.001). No significant difference was found in terms of body mass index between the two groups (p=0.063). Demographic data, chronic diseases, geriatric syndromes and muscle parameters of patients with/without sarcopenia are shown in Table 1.

When we compared the blood parameters representing inflammation of the two groups, CRP, MHR and SIRI values were found to be significantly higher in the sarcopenia group (p=0.006; p<0.001; p=0.001; respectively), but no significant difference was found in terms of platelet indices (MPV/Plt, PDW/Plt, PLR) between the groups (p=0.605; p=0.920; p= 0.510). Table 2 shows the comparison of blood parameters of patients with/without sarcopenia.

The multivariate logistic regression analysis of risk factors for sarcopenia in geriatric patients, including odds ratio (OR) is performed in table 3 and table 4. Among the markers we studied, MHR and SIRI were analysed separately by multivariate regression with age, MMSE, MNA and CKD. In the regression analysis with MHR, MHR (OR: 1.248, 95% CI: 1.562–5.378, p= 0.001) and low MNA score (OR: 1.056, 95% CI: 0.775–0.923, p<0.001) were independently associated with sarcopenia, whereas SIRI (OR: 1.435, 95% CI: 1.044–1.971, p= 0.026) and MNA (OR: 0.835, 95% CI: 0.766–0.909, p<0.001) were independently associated in the analysis with SIRI.

We performed receiver operating characteristic (ROC) curve analysis for MHR and SIRI, and showed that the optimum MHR cut-off point for patients with sarcopenia was 0.99 with 72.2% sensitivity and 55.7% specificity (95% confidence interval (CI): 0.604–0.746, area under the curve (AUC): 0.675, p<0.001). For SIRI the optimum cut-off point was found 1.20 with 60.8% sensitivity and 53% specificity (95% CI: 0.523–0.679, AUC: 0.601, p=0.010) (Fig. 1).

Discussion

Although sarcopenia is still full of unknowns, researchers emphasise low-grade chronic inflammation in its pathophysiology. From this point of view, we investigated the relationship between sarcopenia and inflammatory blood indices, which can be easily obtained from routine blood tests in clinical practice. In the literature, there are studies investigating the relationship between MHR, SIRI, platelet parameters (MPV/Plt, PDW/Plt and PLR) and many inflammatory diseases, but no study investigating their relationship with primary sarcopenia has been found. Therefore our study filled a gap in the literature demonstrating that MHR and SIRI, noninvasive, cost-effective, and easily accessible inflammatory markers, are associated with sarcopenia in geriatric patients.

Tab. 1. Demographic data, chronic diseases, geriatric syndromes and muscle parameters of patients with/without sarcopenia.

	Patients with sarcopenia (n=79)	Patients without sarcopenia (n=183)	p
Female (n, %)	53 (67%)	133 (72%)	0.853
Age, mean±SD	79.59±7.19	75.24±6.91	**<0.001**
Hypertension (n, %)	54 (68%)	140 (76%)	0.167
Diabetes mellitus (n, %)	38 (48%)	69 (37%)	0.116
Heart failure (n, %)	9 (11%)	11 (%6)	0.132
Chronic kidney disease (n, %)	8 (10%)	6 (3%)	**0.034**
Chronic obstructive pulmonary disease (n, %)	10 (12%)	13 (7%)	0.145
Hypothyroidism (n, %)	6 (7%)	35 (%19)	**0.018**
Osteoporosis (n, %)	28 (%35)	51 (27%)	0.220
Parkinson disease (n, %)	7 (%9)	13 (%7)	0.593
Depression (n, %)	15 (19%)	47 (25%)	0.242
Urinary incontinence (n, %)	15 (19%)	24 (13%)	0.220
Delirium (n, %)	5 (6%)	1 (1%)	**0.010**
MMSE, mean±SD	23.95±4.91	26.28±3.50	**<0.001**
MNA, mean±SD	20.95±4.74	24.38±3.71	**<0.001**
GDS, mean±SD	6.26±3.87	4.18±3.84	**<0.001**
Mobility, mean±SD	3.08±2.33	4.95±1.76	**<0.001**
ADLs, mean±SD	2.66±3.32	1.23±2.30	**0.001**
IADLs, mean±SD	11.69±6.08	13.78±4.41	**0.014**
Body mass index (kg/m^2), mean±SD	27.44±6.60	28.89±4.93	0.063
Calf circumference (cm), mean±SD	35.84±6.55	37.79±5.88	**0.026**
Handgrip strength (kg), mean±SD	13.72±5.20	22.83±9.99	**0.001**
Gait speed (m/sn), mean±SD	0.42±0.21	0.6±0.42	**0.001**

MMSE – *Mini-Mental* State *Examination*; MNA – Mini-Nutritional Assessment; GDS – Geriatric Depression Scale; ADLs – Activities of Daily Living; IADLs – Instrumental Activities of Daily Living.
Significant p values are bolded. p<0.05 was considered statistically significant.

Tab. 2. Comparison of blood parameters of patients with/without sarcopenia.

	Patients with sarcopenia (n=79)	Patients without sarcopenia (n=183)	p
SIRI, mean±SD	1.84±1.22	1.39±0.92	**0.001**
MHR, mean±SD	1.46±0.72	1.06±0.54	**<0.001**
MPV/Plt, mean±SD	3.93±1.73	3.82±1.45	0.605
PDW/Plt, mean±SD	7.20±2.62	7.16±2.37	0.920
PLR, mean±SD	156.27±66.86	150.02±71.65	0.510
CRP (mg/L), mean±SD	5.78±5.04	4.21±3.75	**0.006**
ESR (mm/hour), mean±SD	21.05±11.66	19.15±12.19	0.256
Hemoglobin (g/dL), mean±SD	11.98±1.61	12.87±1.48	**<0.001**
Neutrophils (10^3/μL), mean±SD	4.58±1.66	4.28±1.43	0.146
Monocytes (10^3/μL), mean±SD	0.63±0.21	0.53±0.16	**<0.001**
Lymphocytes (10^3/μL), mean±SD	1.86±0.81	1.89±0.63	0.740
Platelet (10^3/μL), mean±SD	261.88±90.11	254.82±78.49	0.524
High-density lipoprotein (mg/dL), mean±SD	47.36±12.49	55.37±16.16	**<0.001**
Low-density lipoprotein (mg/dL), mean±SD	117.75±38.10	135.98±42.46	**0.001**

MPV/Plt – Mean platelet volume / Platelet Ratio; PDW/Plt – Platelet Distribution Width / Platelet ratio; PLR – Platelet / Lymphocyte Ratio; MHR – Monocyte / High-density lipoprotein ratio; SIRI – Systemic inflammation response index, CRP – C-reactive protein; ESR – erythrocyte sedimentation rate. Significant p values are bolded. p<0.05 was considered statistically significant.
* Mean±standard deviation (SD)

To our knowledge, our study is the first to reveal the association of these noninvasive, cost-effective, and easily accessible inflammatory markers (SIRI and MHR) with primary sarcopenia. However, no significant relationship was found between platelet indices and primary sarcopenia. Further large-scale studies on platelet parameters are needed.

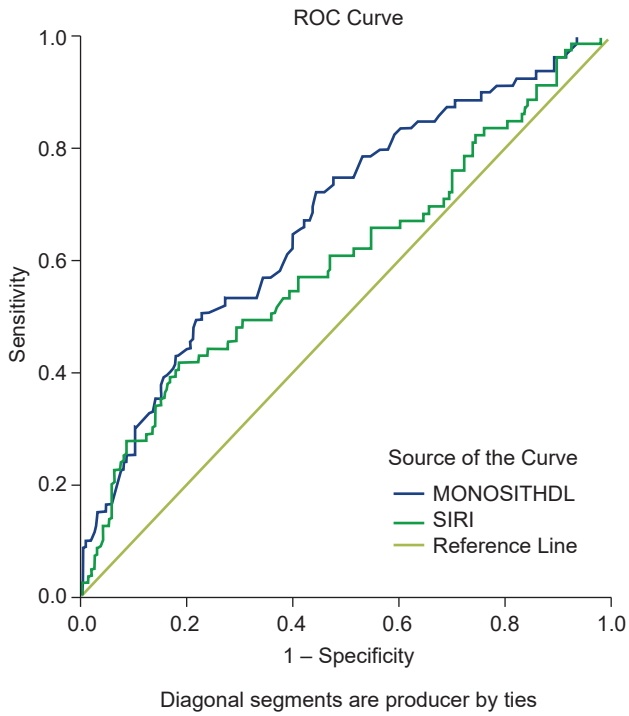

Fig. 1. ROC curves based on a univariate model showing the power of MHR and SIRI to predict sarcopenia. The area under the curve was 0.675 for MHR and 0.601 for SIRI.

It is known that geriatric syndromes have common risk factors, cause common adverse conditions and are related to each other. All of them are thought to have underlying chronic low-grade inflammation (16). We found the frequency of cognitive impairment, malnutrition, and possible depression higher in the sarcopenia group (p<0.001, for all). In a study the risk of developing sarcopenia in geriatric patients with malnutrition was approximately 4-fold higher at four-year follow-up than those without malnutrition (17). In a systematic review and meta-analysis, a significant association between sarcopenia and cognitive impairment risk was found (18). In addition, in our study patients with sarcopenia were more dependent on both basic and instrumental activities of daily living (p=0.001; p=0.14; respectively). It should not be surprising that sarcopenia leads to this outcome as it limits the mobility of patients and it should be kept in mind that decreased mobility may cause sarcopenia.

Inflammatory cytokines are known to accelerate muscle loss, decrease dietary intake, stimulate protein catabolism and suppress

Tab. 3. Multivariate logistic regression analysis of risk factors including SIRI for the prediction of sarcopenia.

	Multivariate LR	
	Odds Ratio (95% CI)	*P*
SIRI	1.435 (1.044–1.971)	**0.026**
Age	1.030 (0.976–1.087)	0.281
MMSE	0.954 (0.873–1.042)	0.292
MNA	0.835 (0.766–0.909)	**<0.001**
CKD	1.692 (0.395–7.238)	0.478
Delirium	1.374 (0.115–16.432)	0.802

LR – Logistic Regression; CI – Confidence interval; SIRI – Systemic inflammation response index; MMSE – *Mini-Mental* State *Examination*; MNA – Mini-Nutritional Assessment; CKD – Chronic kidney disease. Significant p values are bolded. p<0.05 was considered statistically significant

muscle synthesis. Although there are studies in the literature that could not find a relationship between inflammatory parameters and sarcopenia, many studies support the inflammatory background (19). Xiong et al. found a strong relationship between sarcopenia and IL-17, an inflammatory cytokine, in a study of 262 patients aged 61–90 years (5). In our study, increased CRP, MHR, and SIRI also support the idea of low-grade chronic inflammation in sarcopenia in geriatric patients ($p=0.006$; $p<0.001$; $p=0.001$, respectively).

Monocytes are one of the most crucial elements of the inflammatory process and HDL plays an important anti-inflammatory and antioxidant role by controlling the activation of monocytes, preventing macrophage migration, and inhibiting the oxidation of low-density lipoprotein. The balance between them determines inflammation-anti-inflammation-antioxidation status (20). SIRI assesses the balance between systemic inflammation and immune response in the body and is thought to have a better impact in reflecting the inflammatory state. Previous studies have confirmed that SIRI was more comprehensive and effective in evaluating inflammation levels and correlated with the prognosis of chronic diseases (21). As for the components of SIRI, in addition to the proinflammatory roles of monocytes, it is also well established that the systemic inflammatory response is associated with the presence of neutrophilia with a relative lymphocytopenia (22). As in our study, various inflammatory indicators were analysed by Wang et al. and MHR and SIRI were found to be associated with metabolic disorders and cardiovascular disease risk (23).

The results of previous studies on the relationship between sarcopenia and platelet indices are controversial. In those studies the patient population had serious underlying diseases such as cancer or limb threatening ischaemia (24). Furthermore, the diagnosis of sarcopenia in these studies was usually based on muscle mass and not on the new diagnostic criteria for sarcopenia, which prioritise muscle strength. The results of a study in which the study population consisted of 384 Chinese community-dwelling elderly and the diagnosis of sarcopenia was made according to new criteria like ours support our study and showed that PLR cannot be used as a biomarker of sarcopenia (25). Our study demonstrated that MPV/Plt, PDW/Plt and PLR cannot be used as diagnostic biomarkers of sarcopenia.

The present study had some strengths. In the study, we measured platelet parameters, MHR and SIRI which use common peripheral blood counts to reflect inflammatory status and include immunological effects instead of traditional inflammatory cytokines. It is an important advantage that MHR and SIRI are easily accessible markers that can be calculated from blood parameters routinely used in clinical practice. Considering the difficulty and complexity of the diagnosis of sarcopenia, it is very valuable that these simple markers may be warning signs for sarcopenia. This is the first study to reveal the association of these inflammatory markers with sarcopenia. The study also has some limitations. First, this study is a cross-sectional study and has a limitation in the causal explanation of inflammation and sarcopenia. Second, other inflammatory biomarkers (such as IL-1, IL-6, and TNF-α) that we can compare with MHR or SIRI were not examined in our study. And the last limitation is that due to the limited sample size, no validation cohorts were established, which distorted the external authenticity of the result.

Conclusion

Our study showed that MHR and SIRI were associated with sarcopenia in geriatric patients emphasising the role of chronic systemic inflammation in the pathophysiology of sarcopenia. MHR and SIRI appear to be promising markers to economically and practically detect activation of the inflammatory system in sarcopenia and perhaps to assess the aetiology of sarcopenia. A better understanding of the relationship between inflammation and sarcopenia may provide clinical implications for the management and treatment of sarcopenia in geriatric patients.

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