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# The role of elevated monocyte and high-density lipoprotein cholesterol ratio in endothelial dysfunction and cardiovascular risk in acromegaly patients

**Mustafa Aydemir, Ramazan Sarı**

Division of Endocrinology and Metabolism, Department of Internal Medicine, Faculty of Medicine, Akdeniz University, Antalya, Turkiye

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## ABSTRACT

**Aims:** This study aimed to investigate the role of the monocyte-to-high-density lipoprotein ratio (MHR) as an indicator of endothelial dysfunction and cardiovascular risk in patients with acromegaly.

**Methods:** The study group consisted of 125 patients diagnosed with acromegaly, while the control group included 123 healthy individuals who visited the endocrine clinic due to pituitary incidentaloma but had no acromegaly diagnosis. Medical and laboratory records of all participants were reviewed retrospectively.

**Results:** The average MHR in patients with acromegaly was found to be statistically significantly higher than that in the healthy control group. In the acromegaly group, systolic blood pressure, glucose, HbA1c, lipids (total cholesterol, LDL, triglycerides), sedimentation rate, CRP, and neutrophils were significantly higher to the control group. The optimal MHR cutoff for acromegaly was 12.01, with 85.1% sensitivity, 85% specificity, and an AUC of 0.64.

**Conclusion:** MHR, a potential biomarker considered an indicator of inflammation, was significantly higher in patients with acromegaly compared to the healthy control group. This finding suggests that MHR may serve as a useful marker for assessing cardiovascular risk and endothelial dysfunction in patients with acromegaly.

**Keywords:** Acromegaly, monocyte to HDL cholesterol ratio, cardiovascular risk, cardiovascular markers

## INTRODUCTION

Acromegaly is a chronic endocrine disorder caused by persistently elevated levels of growth hormone (GH) and insulin-like growth factor-1 (IGF-1). These hormonal imbalances can lead to widespread effects on various organ systems, particularly the cardiovascular system.[1,2] Regardless of the underlying cause, patients with acromegaly have an increased risk of developing metabolic complications such as dyslipidemia, hypertension, and insulin resistance. All of these conditions are closely related to an increased risk of cardiovascular disease.[3-5]

The monocyte-to-HDL cholesterol ratio (MHR) has emerged as a novel and accessible biomarker for predicting systemic inflammation and cardiovascular risk.[6] Monocytes play a key role in atherosclerotic plaque formation, while HDL cholesterol is known for its anti-inflammatory and cardioprotective properties. A high MHR reflects an imbalance between pro-inflammatory and anti-inflammatory mechanisms, making it a valuable prognostic marker for cardiovascular complications.[7]

The health of the endothelium, a thin layer of cells lining the blood vessels, is critical for overall vascular function. Endothelial cells regulate blood flow, manage coagulation processes, and modulate immune and inflammatory responses.[8] When these cells are damaged or dysfunctional, a range of issues can arise, including the onset and progression of atherosclerosis.[9] Endothelial dysfunction is increasingly recognized as one of the earliest markers of cardiovascular disease. It directly contributes to the development of serious events such as hypertension, plaque accumulation in arteries, heart attacks, and strokes. In this context, the assessment of markers like MHR becomes increasingly important, as they reflect the underlying inflammatory state that can lead to endothelial damage.[10,11]

MHR is rapidly becoming a valuable biomarker in cardiovascular research and clinical practice.[12] By dividing the monocyte count by HDL cholesterol levels, healthcare providers can quickly assess a patient's inflammatory and lipid profile.[13] A high MHR is associated with an increased risk of cardiovascular events, particularly in individuals with chronic illness or those with ambiguous traditional risk factors.[14] This is especially relevant in populations such as acromegaly patients, who are already facing increased metabolic and cardiovascular stress. In these patients, traditional lipid

**Corresponding Author:** Mustafa Aydemir, mustafactf@gmail.com

panels may not fully reflect the inflammatory burden or may be insufficient in predicting future complications. MHR can serve as an additional tool that may enhance early diagnosis and better inform treatment decisions.[5,14-16]

Relationship between MHR and endothelial dysfunction: Monocytes (a type of white blood cell) play an important role in the body's immune and inflammatory responses. When their levels rise (as captured in MHR), they can damage the endothelial cells that line our blood vessels.[17-19] This damage impairs the normal functions of the endothelium, such as controlling blood flow and vascular tone. When the endothelium is constantly under inflammatory stress, it creates a favorable environment for the development of atherosclerosis. Atherosclerosis is the buildup of plaques in the arteries and is one of the underlying factors behind heart attacks and strokes. Simply put, higher monocyte levels mean more inflammation, which damages blood vessels and increases the risk of serious cardiovascular issues.[13]

### Underlying Mechanisms Behind the Relationship between MHR and Cardiovascular Risk

Inflammation plays a central role in the pathogenesis of cardiovascular diseases. Monocytes, as a significant component of the immune system, initiate and sustain inflammatory responses.[20-22] In acromegaly, chronic inflammation resulting from excessive growth hormone secretion can lead to increased monocyte counts, resulting in endothelial damage and elevated cardiovascular risk.[23,24]

### Cholesterol Metabolism and MHR

HDL cholesterol helps remove excess cholesterol from the blood by preventing plaque buildup in the arteries. However, in patients with acromegaly, HDL cholesterol levels are typically low, disrupting the balance between monocytes and HDL cholesterol. This imbalance contributes to the increase in MHR and cardiovascular risk.[25,26]

### Acromegaly Increases Cardiovascular Risk

In acromegaly, the body produces excessive amounts of GH, and this excess affects not only height or physical characteristics but also has significant effects on the cardiovascular system. GH can lead to arterial stiffness (vascular rigidity or atherosclerosis), reducing the elasticity of blood vessels and making it difficult for the body to regulate blood pressure.[27,28] Additionally, GH alters the body's lipid profile, often leading to abnormal cholesterol levels and hypertension. These changes accelerate the development of cardiovascular diseases and increase the risk of life-threatening events such as heart attacks and strokes.[28]

Besides GH, other factors commonly seen in acromegaly patients, such as insulin resistance, obesity, and dyslipidemia, further exacerbate cardiovascular risk.[5] These metabolic abnormalities worsen endothelial dysfunction, facilitating the progression of cardiovascular diseases.

In the context of acromegaly, the effects of GH and IGF-1 levels on MHR have not yet been fully elucidated. This study aims to investigate potential differences in MHR among acromegaly patients and assess its relationship with cardiovascular risk. Thus, it seeks to provide a deeper understanding of the role of MHR as a prognostic marker for cardiovascular diseases associated with GH and IGF-1 levels.

Understanding the potential role of MHR in predicting cardiovascular risk in acromegaly patients may contribute to the development of early intervention strategies for this population. In this context, large-scale and long-term studies in the future could provide further evidence to support the clinical utility of MHR.

## METHODS

### Ethical Considerations

Ethical approval was obtained from the Akdeniz University Faculty of Medicine Human Researches Ethics Committee (Date: 30.01.2025, Decision No: TBAEK-131). All procedures comply with the provisions of the Declaration of Helsinki.

### Study Design

Retrospective medical records of acromegaly patients (72 women and 53 men) were used. These patients were admitted to the Akdeniz University Faculty of Medicine Endocrinology outpatient clinic between 2014 and 2024 due to symptoms of acromegaly or incidental pituitary adenomas.

### Dataset Profile

We collected the following parameters from the medical records and laboratory archives; age, sex, any chronic/systemic disease, CRP, total cholesterol (TC), triglyceride (TG), LDL cholesterol, HDL cholesterol, glycosylated hemoglobin A1c, serum creatinine.

The study group comprised of 125 patients with acromegaly (72 females, 53 men, with a mean age of 56.51±13.04 years) randomly selected from the Endocrinology referral center of the Hospital of Clinics of the Akdeniz University of Antalya. The control group comprised of an approximately 1:1 sample of 123 ambulatory patients without acromegaly (71 females, 52 males 56±13 years) who were matched for age, sex and CV disease risk factors, namely hypertension, diabetes mellitus, dyslipidemia, body-mass index (BMI) and smoking.

All participants underwent a thorough physical examination, including measurement of BMI and blood pressure (BP), according to standard methods.[29,30] All medications in use were recorded. Framingham's global CV risk score (FRS) was estimated for all of them.[31] Risk factors evaluated for the FRS were age, total cholesterol and HDL cholesterol, systolic BP, hypertension, and diabetes status.[31] Acromegaly was diagnosed based on the presence of clinical features in addition to biochemical evidence of GH excess: IGF-1 levels above age-adjusted reference range and lack of suppression of GH to <1 μg/L following documented hyperglycemia during an oral glucose load.[32]

### Study Design and Population

This cross-sectional, comparative study was conducted to investigate the relationship between the MHR and cardiovascular risk across acromegaly. Patients diagnosed with acromegaly. A total of (number) patients who met the inclusion criteria were included in the study.

### Inclusion and Exclusion Criteria

Patients were included if they were aged 18 years or older, had a confirmed diagnosis of acromegaly based on biochemical and radiological findings, and provided informed consent. Exclusion criteria included the presence of active infections, chronic inflammatory diseases (e.g., rheumatoid arthritis), recent steroid use (unrelated to Cushing's syndrome), pregnancy, or severe organ dysfunction (e.g., end-stage renal or hepatic disease).

### Data Collection and Laboratory Measurements

Demographic and clinical data, including age, sex, BMI, and blood pressure, were recorded. Blood samples were collected after an overnight fast for biochemical analyses.

**Monocyte count:** Monocyte levels were measured using an automated hematology analyzer (model and manufacturer).

**HDL cholesterol:** HDL cholesterol levels were measured using an enzymatic colorimetric method (specific kit and manufacturer).

**MHR calculation:** The MHR was calculated by dividing the monocyte count by the HDL cholesterol level (mg/dl).

Other laboratory parameters, such as fasting blood glucose, total cholesterol, triglycerides, C-reactive protein (CRP), and sedimentation rate, were also measured to assess metabolic profiles.

### Cardiovascular Risk Assessment

Cardiovascular risk was assessed using clinical and laboratory markers such as blood pressure, lipid profiles, and glucose metabolism parameters.

### Statistical Analysis

All statistical analyses of this study were performed with SPSS for Windows 22.0 package program (SPSS Inc., Chicago, IL). The Kolmogorov-Smirnov test was used to test normality of distribution. Pearson's Chi-square test was performed for categorical data analyses. We compared parametric values among groups by student's T test. Comparisons of non-parametric values among groups were performed by the Mann-Whitney U Test. Receiver operating characteristic (ROC) curve analysis was used to compare the prognostic powers of the MHR for DRP. $p<0.05$ was considered statistically significant.

## RESULTS

### Patients Demographics

One hundred twenty-five acromegaly patients (72 females and 53 males) who had were eligible for the study. Similarly, 123 control patients (71 females and 52 males) without acromegaly healthy subjects determined as control groups. Patients with acromegaly were regarded as Group 1, healthy subjects were regarded as group 2. The mean age of patients was 56.51±13.04 years in acromegaly patients, and 56.10±10.87 years in healthy subjects. There were no statistical differences between the two groups in terms of age and gender (p=0.725 and p=0.999, respectively).

All laboratory parameters (monocyte counts, HDL cholesterol, and MHR) are summarized in **Table**. The monocyte counts were significantly different between two groups (p=0.043). While monocyte counts were significantly higher in acromegaly patients.

During follow-up, five patients with acromegaly were reported as deceased. Among them, four deaths were attributed to cardiovascular complications, while one patient succumbed to post-Whipple surgery due to malignancy associated with acromegaly.

Compared to the control group, systolic blood pressure, glucose, HbA1c, and lipid parameters (total cholesterol, LDL cholesterol, and triglycerides), as well as sedimentation rate, CRP, and neutrophil levels, were found to be significantly elevated. In contrast, the acromegaly group's HDL cholesterol and hemoglobin levels were significantly lower. However, diastolic blood pressure, creatinine, lymphocyte count, and platelet levels showed no statistically significant differences between the two groups.

**Table. Demographic characteristics of the patients**

| | Control group, n: 123 | Acromegaly n: 125 | p |
|---|---|---|---|
| Age | 56.10±10.87 | 56.51±13.04 | 0.725 |
| Female/male | 71 (57.7%)/52 (42.2%) | 72 (57.6%)/53 (42.4%) | 0.999 |
| Acromegaly duration (years) | - | 14.6±8.10 | |
| Diabetes mellitus | - | 73 (58.4%) | |
| Hypertantion | - | 33 (26.4%) | |
| Hyperlipidemia | - | 55 (44%) | |
| Smoking | 16(125) | 20 (125) | 0.625 |
| BMI (kg/m$^2$) | 24.7±4.1 | 26.17±4.9 | 0.001 |
| Systolic BP mmHg | 116.22±12.66 | 125.05±13.37 | <0.001 |
| Diastolic BP mmHg | 76.82±8.12 | 77.84±9.07 | 0.352 |
| Growth hormone | 0.35±6.6 | 6.50±7.70 | <0.001 |
| IGF-1 | 115±25.66 | 430±252.94 | <0.001 |
| Glucose (mg/dl) | 92±13 | 142.65±83.73 | <0.001 |
| HbA1c (%) | 5.40±1.10 | 6.75±1.66 | <0.001 |
| Creatinin (mg/dl) | 0.83±0.17 | 0.86±0.50 | 0.410 |
| Total cholesterol (mg/dl) | 185.01±27.01 | 211.25±44.04 | 0.001 |
| LDL-C (mg/dl) | 113.04±24.06 | 128.11±35.31 | 0.001 |
| Trigliserit (mg/dl) | 143.21±50.60 | 206.28±125.55 | <0.001 |
| HDL-C (mg/dl) | 47.85±72.81 | 44.70±11.82 | 0.004 |
| Monocyte (/L) | 496±0.15 | 523.56±150.34 | 0.043 |
| MHR | 10.37±4.21 | 12.43±4.64 | 0.001 |
| ESR (mm/h) | 7.02±3.02 | 21.45±14.38 | 0.001 |
| CRP (mg/dl) | 1.30±1.61 | 8.21±24.66 | 0.002 |
| Hemoglobine (g/dl) | 13.32±1.42 | 12.80±1.76 | 0.022 |
| WBC (/L) | 7321.81±1685.21 | 7327.91±2000.22 | 0.973 |
| Neutrophil (/L) | 4610.21±1300.68 | 4280.00±1714.78 | 0.033 |
| Lenfosite (/L) | 2100.82±0.71 | 2317.82±801.21 | 0.060 |
| Platelate (×10$^3$/L) | 261.54±63.80 | 257.55±73.82 | 0.547 |

BMI: Body-mass index, BP: Blood pressure, IGF-1: Insulin-like growth factor-1, WBC: White blood cell, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, HbA1c: Glycated hemoglobin, HDL: High-density lipoprotein, MHR: Monocyte count to HDL ratio

The optimal cutoff value of MHR for acromegaly was 12.01 with 85.1% sensitivity and 85% specificity and an area under the ROCs curve was 0.64, as shown in Figure.

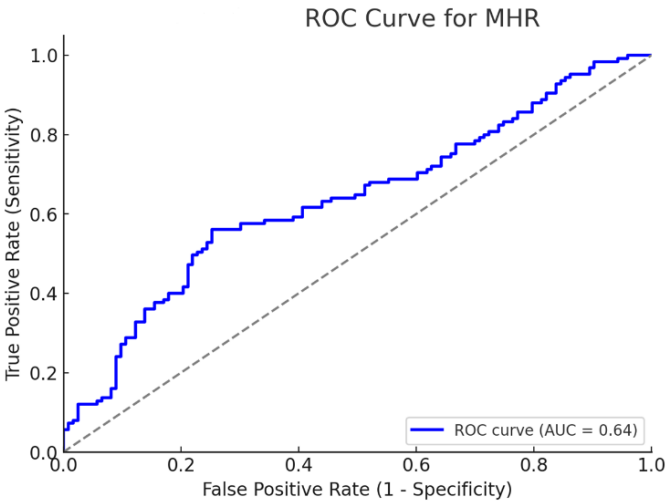


**Figure.** ROC analysis of MHR for acromegaly

ROC: Receiver operating characteristic, MHR: Monocyte count to HDL ratio, HDL: High-density lipoprotein

## DISCUSSION

In this study, we evaluated the MHR and various laboratory parameters in patients with acromegaly compared to healthy controls. Our findings indicate that MHR is significantly elevated in acromegaly patients, suggesting a potential connection between chronic inflammation and lipid metabolism dysregulation in this population.

A key finding of our study is that the optimal cutoff value for distinguishing acromegaly patients from healthy individuals was determined to be 12.01, with a sensitivity of 85.1% and a specificity of 85%. The area under the curve (AUC) of 0.64 suggests a moderate diagnostic value for MHR in acromegaly, which aligns with previous studies that highlight its role as an inflammatory marker in a range of endocrine and metabolic disorders.

Acromegaly is known to be associated with increased cardiovascular risk, as reflected in our results. Monocyte counts, a marker of systemic inflammation, were significantly higher in acromegaly patients compared to the control group (p=0.043). Additionally, levels of systolic blood pressure, glucose, HbA1c, and lipid parameters (total cholesterol, LDL cholesterol, and triglycerides) were significantly elevated in acromegaly patients, while HDL cholesterol levels were lower. These findings indicate a pro-inflammatory and atherogenic state in acromegaly, likely contributing to the increased cardiovascular morbidity and mortality observed in this population.

Importantly, among the acromegaly patients in our study, five were reported deceased, with four deaths attributed to cardiovascular complications. This underscores the necessity of early detection and management of cardiovascular risk factors in patients with acromegaly. Given that MHR is emerging as a marker of inflammation and cardiovascular risk, our findings suggest it could serve as a useful tool for risk stratification in this population.

As there are no prior studies examining the relationship between acromegaly and MHR, we could not make direct comparisons. This study is the first to establish an association between acromegaly and MHR. Monocytes play a crucial role in inflammatory reactions, as they are responsible for secreting pro-inflammatory and pro-oxidant cytokines. Conversely, HDL cholesterol possesses antioxidant and anti-inflammatory properties, including reducing macrophage accumulation, inhibiting monocyte transmigration, increasing nitric oxide synthase expression in endothelial tissues, and protecting endothelial cells.[35]

Recent research has identified the MHR as a promising new marker for inflammation in diabetes and its complications. For example, Gökçay Canpolat et al.[36] observed that MHR levels were higher in diabetic patients with neuropathy compared to those without, although the difference wasn't statistically significant. Karatas et al.[16] found a more noticeable result MHR levels were significantly higher in patients with diabetic nephropathy compared to both diabetics without kidney issues and healthy individuals. Similarly, Onalan et al.[37] reported that MHR levels were significantly elevated in diabetics with kidney damage versus those without it. In our own study focusing on acromegaly patients, we found a specific cutoff value for MHR: 12.01. This value showed a strong ability to detect cardiovascular risk, with a sensitivity of 85.1% and specificity of 85%. The AUC was 0.64, which suggests that MHR has a moderate but meaningful diagnostic value in identifying cardiovascular risk among acromegaly patients.

Interestingly, while monocyte counts, lipid parameters, and inflammatory markers (CRP, sedimentation rate, and neutrophil levels) were elevated in acromegaly patients, no significant differences were observed in diastolic blood pressure, creatinine levels, lymphocyte counts, or platelet levels between the two groups. This suggests that the inflammatory response in acromegaly may be more closely related to monocyte activation and alterations in lipid metabolism rather than generalized immune activation.

Overall, our findings highlight the potential utility of MHR as a biomarker for inflammation and cardiovascular risk in acromegaly. Future studies with larger sample sizes and longitudinal follow-up are warranted to better understand the prognostic significance of MHR and its role in guiding therapeutic strategies for acromegaly patients.

### Limitations

Our study has several potential limitations that should be acknowledged. The first limitation is the relatively small sample size and the retrospective design of the study, which may restrict the generalizability of our findings and introduce potential biases. The second limitation is the incomplete data regarding the medications used by the patients, which precluded an evaluation of the potential effects of pharmacological treatments on the observed outcomes. The third limitation pertains to the presentation of monocyte count as a numerical value, which does not provide information on monocyte activation status. Monocyte activation, which plays a critical role in the pathogenesis of diabetic complications, could offer

deeper insights into the underlying mechanisms but was not assessed in this study. These limitations highlight the need for future prospective studies with larger cohorts, comprehensive medication data, and more detailed assessments of monocyte activation to further elucidate the relationships explored in this research.

## CONCLUSION

Our study shows that the MHR is significantly higher in patients with acromegaly than in healthy individuals. This suggests that inflammation and disrupted lipid metabolism play an important role in the cardiovascular risks linked to acromegaly. MHR may be a useful biomarker for identifying acromegaly patients at greater risk of heart disease. The increase in MHR appears to reflect the impact of excess growth hormone and IGF-1 on cholesterol balance and inflammation. Understanding how inflammation and cholesterol issues interact in acromegaly can lead to earlier diagnosis and more targeted treatments to prevent heart complications. While more research is needed, MHR could become a valuable tool for managing cardiovascular health in acromegaly patients.

## ETHICAL DECLARATIONS

### Ethics Committee Approval

This research received approval from the Akdeniz University Clinical Researches Ethics Committee (Date: 30.01.2025, Decision No: TBAEK-131).

### Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

### Referee Evaluation Process

Externally peer-reviewed.

### Conflict of Interest Statement

The authors have no conflicts of interest to declare.

### Financial Disclosure

The authors declared that this study has received no financial support.

### Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version

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