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Research Article

# Relationship between hematologic inflammatory indices and clinical findings in patients with acromegaly

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## Abstract

**Objectives:** We primarily aimed to investigate the hematologic inflammatory parameters such as mean platelet volume (MPV), neutrophil-lymphocyte ratio (NLR), and platelet–lymphocyte ratio (PLR) in patients with acromegaly. We also aimed to reveal the importance of these parameters in determining disease activity.

**Methods:** The medical data of 535 patients with acromegaly were retrospectively reviewed. The sociodemographic characteristics, presence of comorbid disease, acromegaly-related clinical and medical treatment characteristics, insulin-like growth factor-1 and growth hormone levels at diagnosis, postoperative 3rd month and last visit, and hematologic inflammatory markers and indices at last visit were obtained from the patients' medical charts. The patients were divided into age-, sex-, and comorbid disease-matched four groups according to their last remission status: active disease, remission with only surgery, remission with medication, and discordant disease. Finally, a total of 290 patients were included.

**Results:** We examined a total of 290 patients with acromegaly after primary therapy; 36 had active disease, 77 were in remission with only surgery, 129 were in remission with medication, and 48 had a discordant disease. When the patients were categorized by last remission status, the median MPV was higher in patients with discordant disease than in the remission group with only surgery, and there were no differences in terms of the NLR and PLR between groups. When the participants were divided into two groups according to the presence of remission at the postoperative 3rd month, patients who had remission had lower MPV levels than those who had not. However, the groups had similar features for the NLR and PLR.

**Conclusion:** Our results, particularly those that reveal positive association between MPV and remission status, indicate that subclinical inflammation may play a role in increased mortality and morbidity. Therefore, in addition to patients with active disease, patients with discordant disease should be followed closely for cardiovascular risks.

**Keywords:** Acromegaly, growth hormone, insulin-like growth factor, mean platelet volume (MPV), neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR)

Acromegaly is a rare endocrine disease caused by excessive secretion of growth hormone (GH) by a pituitary adenoma. GH and insulin-like growth factor-1 (IGF-1) mediate many biochemical pathways and promote cell growth [1]. The importance of GH/IGF-1 axis hypersecretion to initiate the inflammatory process through cytokine production has been clearly demonstrated [2, 3]. Also, it is well known that prolonged GH/IGF-1 axis hypersecretion leads to many systemic complications, especially cardiovascular diseases and increased mortality risk [3-5]. These complications have been reported to be associated with chronic inflammation [6-9].

In recent years, easily accessible, inexpensive, and widely used complete blood count (CBC)-derived parameters have been the subject of high interest [10, 11]. Many previous stud-

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ies have shown that these new markers are associated with chronic subclinical inflammation in chronic diseases, such as diabetes [12, 13] and ischemic heart disease [14, 15], and in several cancers such as thyroid [16], adrenal gland [17], neuroendocrine tumors [18]. One of those inflammatory markers, mean platelet volume (MPV), a precise measure of platelet size, is an indicator of platelet function [19]. Increased MPV shows platelet activation and is identified as an independent risk factor for atherosclerotic processes in patients with vascular risk factors such as diabetes, hypertension, and hypercholesterolemia [20, 21]. On the other hand, the new markers, neutrophil-lymphocyte ratio (NLR), and platelet-lymphocyte ratio (PLR), are superior to absolute neutrophil, lymphocyte, and platelet counts to show inflammation. While many physiological and pathological factors affect the number of these blood components, these ratios remain stable [22].

In the literature, the data on hematologic parameters in patients with acromegaly are limited. There are studies addressing that some inflammatory markers such as MPV, interleukin 8 (IL-8), tumor necrosis factor-alpha, vascular cell adhesion molecule-1, and intercellular adhesion molecule-1 may increase in patients with acromegaly [23-25]. In the present study, we primarily aimed to investigate the hematologic inflammatory parameters such as MPV, NLR, and PLR in patients with acromegaly. We also aimed to reveal the importance of these parameters in determining the disease activity.

## Materials and Methods

### Participants and procedure

The medical data of 535 patients with acromegaly who were followed at the Endocrinology, Metabolism and Diabetes outpatient clinic of Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine between 2000 and 2020 were retrospectively reviewed. Patients who had missing information concerning any clinical, biochemical, and radiological features and who received medical therapy or radiotherapy before pituitary surgery were excluded. The patients were divided into age-, sex-, and comorbid disease-matched four groups according to their last remission status: active disease, remission with only surgery, remission with medication, and discordant disease. Finally, a total of 290 patients were included.

Age, sex, presence of any comorbid disease (diabetes, hypertension, dyslipidemia, congestive heart failure, coroner artery disease, and obstructive sleep apnea), age at diagnosis, time to diagnosis, total disease duration, follow-up period, number of pituitary surgery, preoperative maximum tumor size, remission status at the postoperative 3rd month, postoperative medical treatments categorized as a dopamine agonist (DA; cabergoline), somatostatin receptor ligands (SRL; octreotide LAR or lanreotide ATG), and GH receptor antagonist (GHRA; pegvisomant), and duration of these treatments, IGF-1, random/nadir GH at diagnosis and follow-up period, hematologic inflammatory indices such as MPV, NLR, and PLR at the last visit were obtained from the patients' medical charts.

### Endocrinological assessment

The clinical symptoms of acromegaly, pituitary adenoma confirmed by sellar imaging, preoperative age- and the sex-adjusted IGF-1 values that exceed the upper limit of the reference range, and lack of suppression of GH to <0.4 ng/mL at an oral glucose tolerance test (OGTT) were determined as biochemical diagnostic criteria for acromegaly [1]. All the patients with acromegaly underwent pituitary surgery, and the diagnosis was also confirmed with histopathological examination of the tumor. To determine remission status, we measured IGF-1, random GH, and nadir GH at an OGTT at the postoperative 3rd month and last visit. Control of disease activity was determined as normal age- and sex-adjusted serum IGF-1 values, random GH <1.0 ng/mL, or OGTT-nadir GH <0.4 ng/mL [1]. The discordant disease was determined as the presence of abnormal GH levels with IGF-1 values within the reference range ("high GH" discordant type) or elevated IGF-1 and normal GH levels ("high IGF-1" discordant type) [26]. Repeat surgery was performed for patients with active disease with residual lesions. Finally, medical adjuvant therapy was initiated for persistent disease.

### Biochemical analysis

Biochemical parameters, such as IGF-1, GH, and CBC, were collected fasting from 8:00 a.m. to 10:00 a.m. Serum GH and IGF-1 levels were assayed using the electrochemiluminescence immunoassay method using Roche Cobas e systems (Roche, Cobas e 602, Roche Diagnostics GmbH, Mannheim, Germany). Blood counts were analyzed on the Beckman Coulter Unicel DXH 800 analyzer (Beckman Coulter, Miami, FL) immediately after being admitted to the laboratory.

The serum reference ranges provided by our hospital biochemistry laboratory were considered normal (GH: 0.126-9.88 ng/mL in females and 0.03-2.47 ng/mL in males; MPV: 6.9-10.8 fL; neutrophil: 2.1-6.1×$10^3$ $\mu L^{-1}$; lymphocyte: 1.3-3.5×$10^3$ $\mu L^{-1}$; platelet: 156-373×$10^3$ $\mu L^{-1}$). Finally, the IGF-1 levels were assessed according to age- and sex-adjusted reference ranges [27].

### Ethical issues

The study was approved by the local ethics committee of Istanbul University, Istanbul Faculty of Medicine (Decision No.: 681602, Date: January 3, 2022). All procedures performed in studies involving human participants were conducted in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

### Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software (version 21.0). The data were first analyzed for normality using the Shapiro-Wilk test. Continuous variables were expressed as mean ± stan-

**Table 1. Comparison of the sociodemographic characteristics and comorbid disease**

| Characteristics | Active disease n=36) | | Remission with only surgery (n=77) | | Remission with medication (n=129) | | Discordant disease (n=48) | | p |
|---|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | n | % | |
| Age (years), Mean±SD | 46.9±14.9 | | 51.2±9.1 | | 49.9±11.2 | | 49.7±12.4 | | 0.339[a] |
| Sex | | | | | | | | | |
| Male | 18 | 50 | 26 | 33.8 | 57 | 44.2 | 13 | 27.1 | 0.072[b] |
| Female | 18 | 50 | 51 | 66.2 | 72 | 55.8 | 35 | 72.9 | |
| Presence of any comorbid disease | | | | | | | | | |
| Diabetes | 12 | 33.3 | 25 | 32.5 | 35 | 27.1 | 11 | 22.9 | 0.603[b] |
| Hypertension | 11 | 30.6 | 22 | 28.6 | 23 | 17.8 | 8 | 16.7 | 0.135[b] |
| Dyslipidemia | 9 | 25 | 13 | 16.9 | 14 | 10.9 | 10 | 20.8 | 0.131[b] |
| CHF | 1 | 2.8 | 2 | 2.6 | 0 | 0 | 0 | 0 | 0.193[b] |
| CAD | 1 | 2.89 | 7 | 9.1 | 4 | 3.1 | 3 | 6.3 | 0.254[b] |
| OSAS | 5 | 13.9 | 5 | 6.5 | 6 | 4.7 | 1 | 2.1 | 0.119[b] |

[a]: One-way analysis of variance; [b]: Pearson's Chi-squared test. CHF: Congestive heart failure; CAD: Coroner artery disease; OSAS: Obstructive sleep apnea syndrome.

dard deviation (SD) and/or medians [interquartile range (IQR)]. To compare means between groups with normal data distributions, Student's t-test was used for the pairwise comparison, and one-way analysis of variance (ANOVA) was used for the four-group comparison. In groups that do not fit normal distributions, medians were compared using the Mann-Whitney U test for the pairwise comparison and the Kruskal-Wallis test for the four-group comparison. Post hoc tests were then performed to account for errors due to multiple comparisons among groups when necessary. Frequencies were compared using Pearson's Chi-squared, Yates' Chi-squared (continuity correction), and Fisher's exact tests. Spearman's and Pearson's correlation coefficients were calculated for relationships between variables. The results were evaluated at a 95% confidence interval, with a value of $p<0.05$ considered statistically significant.

## Results

### Patients' demographic and clinical characteristics

We examined a total of 290 patients with acromegaly after primary therapy; 36 had active disease, 77 were in remission with only surgery, 129 were in remission with medication, and 48 had discordant disease (high GH type: 44; high IGF-1 type: 4) with a mean age of 49.8±11.5 years. The patients' sociodemographic characteristics and presence of comorbid disease are summarized in Table 1.

The acromegaly-related clinical and medical treatment characteristics are shown in Table 2. In terms of postoperative medical treatments, while there were no differences between groups for the use of DA or GHRA, the use of any SRL was the lowest rate in the discordant disease group. However, the cumulative doses of these medical treatments were similar in each group ($p>0.05$ for all). The comparison of the IGF-1 and GH levels at diagnosis, postoperative 3rd month, and last visit is detailed in Table 3.

### Comparison of the hematologic inflammatory markers and indices

The comparison of the hematologic inflammatory indices at the last visit is summarized in Table 4. When patients were categorized by last remission status, the median MPV levels were higher in patients with discordant disease than in patients with remission with only surgery (9.1 [IQR=8.3-9.6] vs 8.6 [IQR=7.9-9.3], $p=0.019$), there were no differences in terms of the NLR and PLR between groups ($p>0.05$ for all).

When participants were divided into two groups according to the presence of remission at the postoperative 3rd months, patients who had remission had lower MPV levels than those who had not (8.4 [IQR=7.8-9.1] vs 8.7 [IQR=8.1-9.4], $p=0.008$). However, the groups had similar features for the NLR and PLR ($p>0.05$ for all). On the other hand, when patients were separately classified as those who received DA, SRL, or GHRA or not, these hematologic indices were similar between groups ($p>0.05$ for all).

Patients who had any comorbid disease (diabetes, hypertension, dyslipidemia, congestive heart failure, coroner artery disease, and obstructive sleep apnea) had similar MPV, NLR, and PLR values compared with those without ($p>0.05$ for all).

### Correlations of the MPV, NLR, and PLR with IGF-1 and GH

Among all participants, the MPV levels showed weak positive correlation with IGF-1 and random GH at the postoperative 3rd month and last visit (Fig. 1). However, there was no significant correlation between IGF-1 and GH levels at diagnosis and during follow-up and the other indices.

**Table 2. Comparison of the acromegaly-related clinical and medical treatment characteristics**

| Characteristics | Active disease (n=36) | | Remission with only urgery (n=77) | | Remission with medication (n=129) | | Discordant disease (n=48) | | p |
|---|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | n | % | |
| Age at diagnosis (years), Mean±SD | 39.6±12.8 | | 43.3±9.3 | | 39.3±10.7 | | 39.5±11.8 | | 0.061[a] |
| Time to diagnosis (months), (IQR) | 3 (0-12) | | 5 (0-17) | | 5 (0-28) | | 7 (0-36) | | 0.304[a] |
| Total disease duration (months), (IQR) | 81 (28-128) | | 72 (40-123) | | 106 (72-163) | | 93 (60-166) | | **0.002**[a] |
| Follow-up period (months), (IQR) | 62 (23-111) | | 60 (33-108) | | 87 (55-134) | | 65 (28-124) | | **0.003**[a] |
| Preoperative max. tumor size (mm), (IQR) | 24 (14-30) | | 12 (9-20) | | 16 (12-24) | | 22 (13-25) | | **<0.001**[a] |
| Remission at postoperative 3rd month | 2 | 5.6 | 54 | 70.1 | 31 | 24 | 9 | 18.8 | **<0.001**[b] |
| Postoperative medical treatments | | | | | | | | | |
| DA - cabergoline | 16 | 44.4 | NA | NA | 34 | 26.4 | 19 | 39.6 | 0.059[b] |
| SRL - octreotide or lanreotide | 36 | 100 | NA | NA | 127 | 98.4 | 36 | 75 | **<0.001**[b] |
| GHRA - pegvisomant | 4 | 11.1 | NA | NA | 17 | 13.2 | 3 | 6.3 | 0.432[b] |

[a]: Kruskal-Wallis test; [b]: Pearson's Chi-squared test. IQR: Interquartile range; DA: Dopamine agonist; SRL: Somatostatin receptor ligands; GHRA: Growth hormone receptor antagonist; NA: Not available.

**Table 3. Comparison of the IGF-1 and GH levels at diagnosis, postoperative 3rd month, and last visit**

| Characteristics | Active disease (n=36) | Remission with only surgery (n=77) | Remission with medication (n=129) | Discordant disease (n=48) | p* |
|---|---|---|---|---|---|
| | Median (IQR) | | | | |
| Preoperative | | | | | |
| IGF-1 | 638 (351-882) | 511 (344-739) | 697 (522-952) | 797 (495-1170) | **0.008**[a] |
| Random GH | 15.6 (6.6-35.2) | 5.4 (2.3-15.4) | 11.3 (3.4-27.1) | 18.7 (5.3-40) | **0.003**[b] |
| Nadir GH-OGTT | 12.2 (6.2-40) | 3.2 (1.9-10.4) | 8 (2.9-22) | 6.3 (3.1-22.3) | **0.005**[c] |
| Postoperative 3rd month | | | | | |
| IGF-1 | 600 (488-852) | 207 (155-310) | 491 (343-630) | 344 (258-627) | **<0.001**[d] |
| Random GH | 3.3 (0.3-8) | 0.5 (0.2-1.1) | 1.9 (0-5) | 2 (0.7-7.4) | **<0.001**[e] |
| Nadir GH-OGTT | 3.3 (1.6-6.7) | 0.1 (0.1-0.4) | 2 (1-4.7) | 1.6 (0.6-4.4) | **<0.001**[f] |
| Last visit | | | | | |
| IGF-1 | 358 (286-495) | 153 (123-205) | 176 (143-211) | 196 (157-231) | **<0.001**[g] |
| Random GH | 2.5 (1.1-7.6) | 0.4 (0.2-0.7) | 0.5 (0.4-0.8) | 2.2 (1.4-3) | **<0.001**[h] |

All measurements are given in ng/mL. *: Kruskal-Wallis test. Post hoc analysis results (adjusted p-value): [a]: Discordant disease vs remission with only surgery, p=0.12; remission with medication vs remission with only surgery, p=0.025. [b]: Active disease vs remission with only surgery, p=0.021; discordant disease vs remission with only surgery, p=0.007. [c]: Active disease vs remission with only surgery, p=0.004. [d]: Active disease vs discordant disease, p=0.012; active disease vs remission with only surgery, p<0.001; discordant disease vs remission with only surgery, p=0.002; remission with medication vs remission with only surgery, p<0.001. [e]: Active disease vs remission with only surgery, p<0.001; discordant disease vs remission with only surgery, p=0.001; remission with medication vs remission with only surgery, p=0.003. [f]: Active disease vs remission with only surgery, p<0.001; discordant disease vs remission with only surgery, p<0.001; remission with medication vs remission with only surgery, p<0.001. [g]: Active disease vs discordant disease, p<0.001; active disease vs remission with medication, p<0.001; active disease vs remission with only surgery, p<0.001; discordant disease vs remission with only surgery, p=0.029. [h]: Active disease vs remission with medication, p<0.001; active disease vs remission with only surgery, p<0.001; discordant disease vs remission with medication, p<0.001; discordant disease vs remission with only surgery, p<0.001. IGF-1: Insulin-like growth factor; GH: Growth hormone; IQR: Interquartile range; OGTT: Oral glucose tolerance test.

When patients were categorized as the last remission status, in the remission group with only surgery, the MPV levels showed moderate positive correlation with IGF-1 at the postoperative 3rd month and last visit (Fig. 2). In other remission groups, none of the hematologic indices were significantly correlated with IGF-1 and GH levels at diagnosis and during follow-up.

## Discussion

In this study, we primarily determined that patients with acromegaly who had discordant disease had higher MPV levels than those who had remission with only surgery. However, we did not observe any differences in NLR and PLR between

**Table 4. Comparison of the hematologic inflammatory indices at the last visit**

| Characteristics | Active disease (n=36) | Remission with only surgery (n=77) | Remission with medication (n=129) | Discordant disease (n=48) | p* |
|---|---|---|---|---|---|
| | Median (IQR) | | | | |
| MPV | 8.7 (8.1-9.6) | 8.4 (7.9-9.1) | 8.6 (7.9-9.3) | 9.1 (8.3-9.6) | **0.025**[a] |
| NLR | 1.9 (1.5-2.3) | 1.7 (1.3-2.5) | 1.9 (1.4-2.5) | 1.7 (1.4-2.3) | 0.410 |
| PLR | 113.5 (96.9-145.2) | 123 (93.5-150) | 119 (99.2-152) | 108 (89.3-135.7) | 0.125 |

*Kruskal-Wallis test. Post hoc analysis results (adjusted p-value): [a]: Discordant disease vs remission with only surgery, p=0.019. IQR: Interquartile range; MPV: Mean platelet volume; NLR: Neutrophil-lymphocyte ratio; PLR: Platelet-lymphocyte ratio.

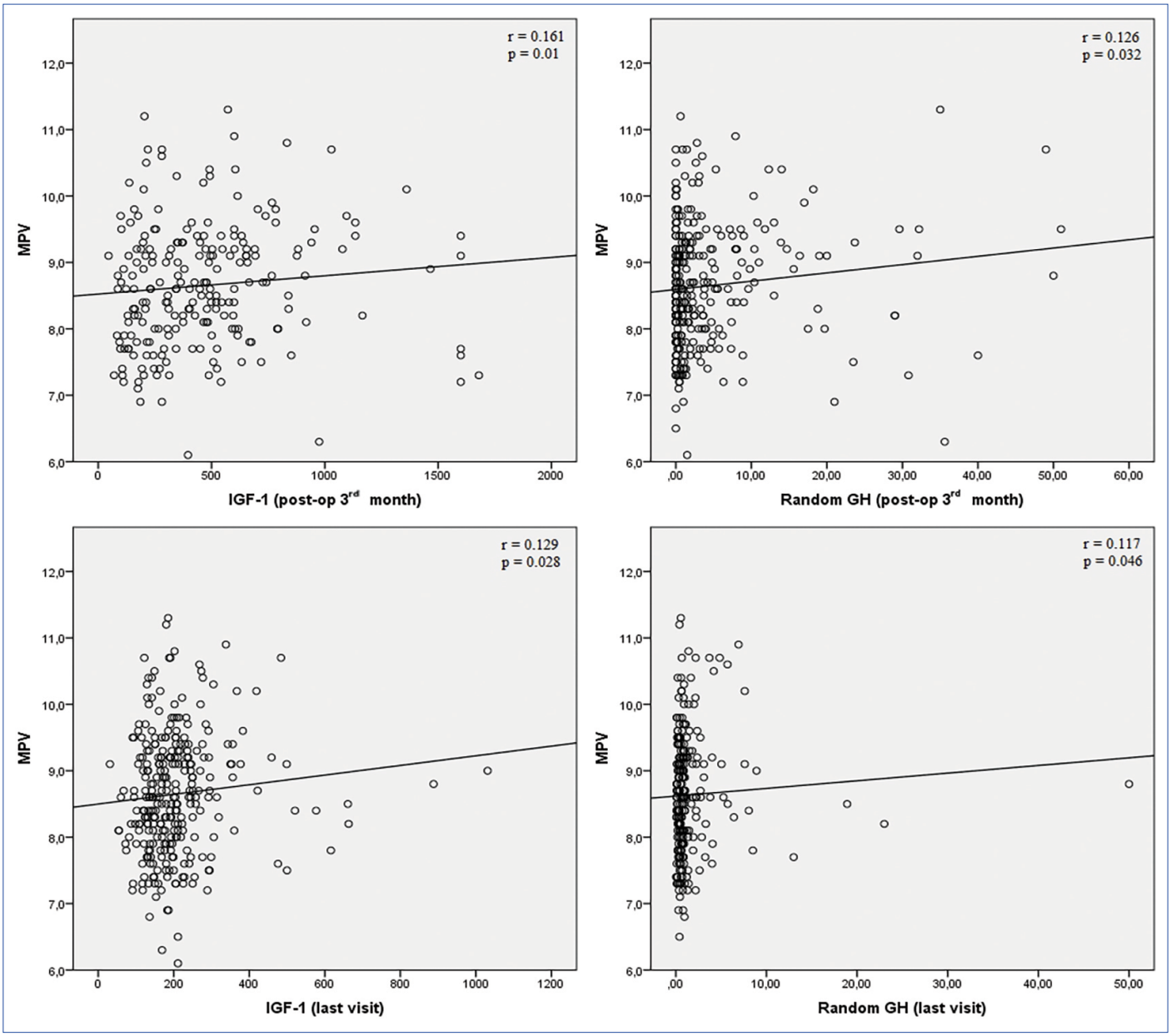


**Figure 1.** The correlations of the MPV with IGF-1 and random GH at the postoperative 3rd month and last visit among all participants.
MPV: Mean platelet volume; IGF-1: Insulin-like growth factor-1; GH: Growth hormone.

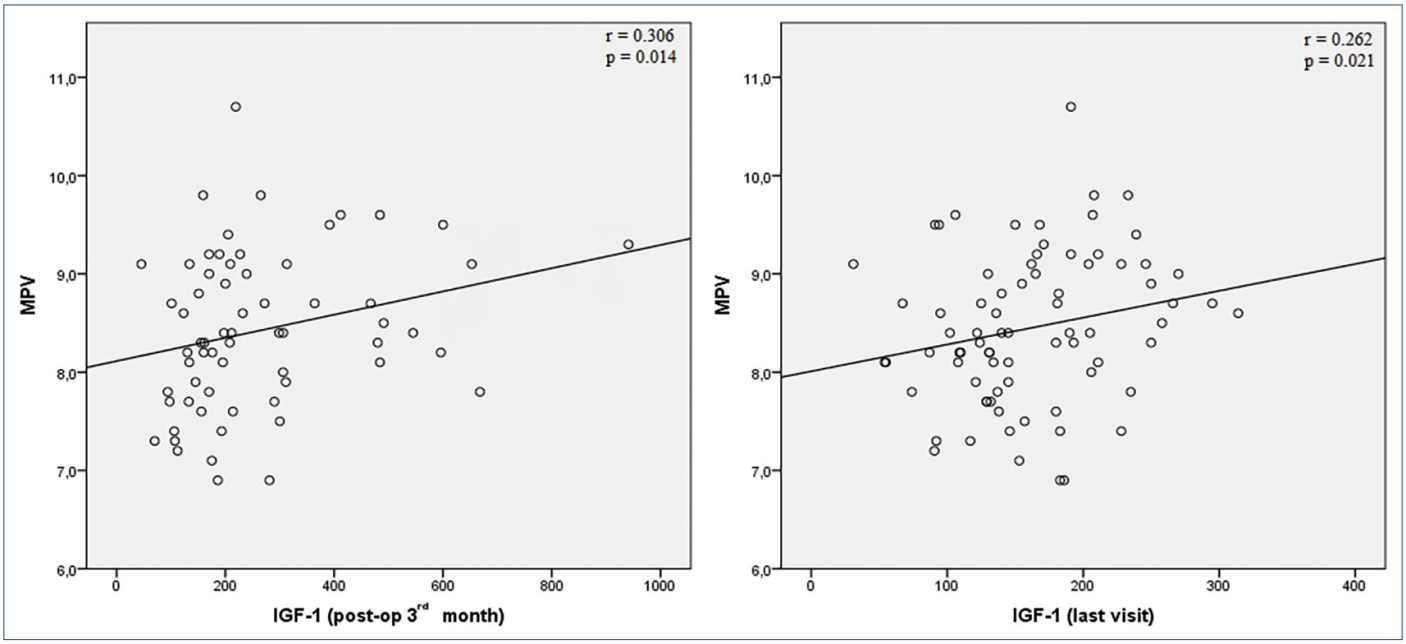


**Figure 2.** The correlations of the MPV with IGF-1 at the postoperative 3rd month and last visit in the group of remission with only surgery.
MPV: Mean platelet volume; IGF-1: Insulin-like growth factor-1.

last remission status groups. On the other hand, we detected that patients who had remission at the postoperative 3rd month had lower MPV levels than those who had not. However, we determined that the presence of remission at the postoperative 3rd month had no effect on NLR and PLR. Finally, we found that whether the patients received DA, SRL, or GHRA or not did not affect any hematologic inflammatory indices.

Regarding MPV levels in patients with acromegaly, conflicting results have been reported in the literature [20, 23, 28-30]. Some authors found that MPV levels were increased in patients with acromegaly compared with the control group [20, 23, 29], while others showed that it was similar [10, 28]. In a cross-sectional study in which 38 patients with acromegaly were divided into three groups according to their remission status 6 months after surgery, MPV values were significantly different between the three groups [29]. In this study, the active disease group had the highest MPV, while remission with only surgery group had the lowest values [29]. Supporting this, in our study, we determined that patients with acromegaly who had discordant disease had higher MPV levels than those who had remission with only surgery. It can be thought that our findings may be useful in demonstrating inflammation in individuals with uncertain disease activity, which is defined as a discordant disease. Besides, in the literature, two previous studies reported striking results regarding the remission with SRL after surgery. In both studies, the authors found a significant decrease in MPV values in patients who were remission without any SRL treatment after surgery, but they did not find any change in MPV levels in patients who were remission with SRL treatment after surgery [29, 30]. All authors explained these results as the risk of atherosclerosis may still be increased although the disease was biochemically controlled with SRL treatment. Also, the relatively small number of patients in these studies may be the main reason for these contradictory results of MPV.

In the literature on patients with acromegaly, studies regarding the levels of circulating blood cell-related inflammatory indices such as NLR, PLR, and their relationship with treatment are conflicting [10, 22, 31]. In our study, we did not observe any difference in the NLR and PLR according to the last remission status. Similarly, in a recent study, it was found that preoperative NLR and values after remission with medical treatment were similar [22]. It can be said that disease control with medical treatment cannot improve the inflammatory state caused by the disease. On the other hand, in the study of Akyay et al. [22] in which NLR values were compared retrospectively, patients with active disease had higher NLR values than controls. In another study, Szydełko et al. [10] reported that the NLR and PLR were significantly higher in acromegaly than in nonfunction pituitary adenomas and controls. These findings can be considered as an example of increased inflammation for naïve active patients with acromegaly.

In the present study, we detected that patients who had remission at the postoperative 3rd month had lower MPV levels than those who had not. Similar to our results, Demirpence et al. [29] revealed that the MPV value was decreased after effective surgical resection. By contrast, in the literature, there are several studies showing no change in MPV levels in patients with remission at the postoperatively 3rd month [10, 20, 30]. Although the results of these studies are not consistent, we can say that the postoperative 3rd month remission generally provides a reduction in inflammation. On the other hand, in our study, we determined that the presence of remission at

the postoperative 3rd month had no effect on NLR and PLR. Similarly, in another study, no significant differences in preoperative and postoperative NLR and PRL values were found in patients with acromegaly [10]. In contrast, Akyay et al. [22] showed that patients who were cured postoperative 3rd month had a significant reduction in NLR. Also, we found that whether the patients received DA, SRL, or GHRA or not did not affect any hematologic inflammatory indices. Our results were consistent with Szydełko et al.'s [10] study.

In several previous studies, the analyses showed a positive correlation between IGF-1, GH, MPV, NLR, and PRL [23, 31]. Similarly, we found that the IGF-1 and GH at the postoperative 3rd month and last visit showed positive correlation with MPV, but not with NLR and PLR. It can be said that long-term IGF-1 exposure increases atherosclerotic risk markers. On the other hand, some studies did not find any positive correlation between these parameters [10, 22]. No significant correlation in these studies was because of the small sample size.

To the best of our knowledge, our study has the largest sample size to address hematologic inflammatory indices in patients with acromegaly. Also, this is the first study in which patients with discordant disease were evaluated as a separate group. On the other hand, this study had several limitations. First, active and discordant disease groups had a relatively low sample size. Second, due to the cross-sectional nature of the study, some clinical measurements such as blood pressure and body mass index were not assessed. For this reason, it can be thought that hematologic indices may be affected by these measurements. Finally, for more precise results, our findings need to be tested in prospective studies evaluating the change of hematologic inflammatory indices with larger samples of patients with acromegaly.

## Conclusion

The findings of the present study, revealing a positive association between MPV and remission status, indicates that subclinical inflammation may play a role in the increased mortality and morbidity due to uncontrolled IGF-1 levels in acromegaly. Therefore, in addition to patients with active disease, patients with discordant disease should be followed closely in terms of cardiovascular risks. Finally, further prospective studies are needed to expand the clinical use of these hematologic indices.

**Conflict of Interest:** The authors declare that there is no conflict of interest.

**Ethics Committee Approval:** The study was approved by The Istanbul University, Istanbul Faculty of Medicine Clinical Research Ethics Committee (No: 681602, Date: 03/01/2022).

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