Prognostic factors for steroid-free remission in patients with idiopathic inflammatory myopathies: importance of anthropometric measurements

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Abstract

Background: Several studies have been conducted on factors associated with mortality in idiopathic inflammatory myopathies (IIMs), but few studies have assessed prognostic factors for steroid-free remission in IIM. We investigated the various clinical factors, including body measurements, that affect IIM treatment outcomes.

Methods: Patients who were newly diagnosed with IIM between 2000 and 2018 were included. Steroid-free remission was defined as at least 3 months of normalisation of muscle enzymes and no detectable clinical disease activity. The factors associated with steroid-free remission were evaluated by a Cox regression analysis.

Results: Of the 106 IIM patients, 35 displayed steroid-free remission during follow-up periods. In the multivariable Cox regression analyses, immunosuppressants’ early use within 1 month after diagnosis [hazard ratio (HR) 6.21, 95% confidence interval (CI) 2.61–14.74, \( p < 0.001 \)] and sex-specific height quartiles (second and third quartiles versus first quartile, HR 3.65, 95% CI 1.40–9.51, \( p = 0.008 \) and HR 2.88, 95% CI 1.13–7.32, \( p = 0.027 \), respectively) were positively associated with steroid-free remission. Polymyositis versus dermatomyositis (HR 0.21, 95% CI 0.09–0.53, \( p = 0.001 \)), presence of dysphagia (HR 0.15, CI 0.05–0.50, \( p = 0.002 \)) and highest versus lowest quartile of waist circumference (WC; HR 0.24, 95% CI 0.07–0.85, \( p = 0.027 \)) were negatively associated with steroid-free remission.

Conclusion: The early initiation of immunosuppressant therapy, type of myositis and presence of dysphagia are strong predictors of steroid-free remission in IIM; moreover, height and WC measurements at baseline may provide additional important prognostic value.

Keywords: height, idiopathic inflammatory myopathies, immunosuppressant, treatment outcome, waist circumference

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Introduction

Idiopathic inflammatory myopathies (IIMs) are systemic autoimmune disorders characterised by muscle weakness and inflammation.\(^1\) Some patients have a monocyclic disease course, but \( \geq 50\% \) of patients experience a chronic continuous course.\(^2\) High-dose corticosteroids are the first line of treatment empirically in most IIM patients, but there are no clear evidence-based guidelines for tapering and discontinuing the use of corticosteroids even though various adverse events of long-term corticosteroid use have resulted in harmful effects on health outcomes.\(^3\) Several studies have reported on the factors associated with deterioration and death related to IIM, including malignancy, interstitial lung disease, pulmonary infection and old age.\(^4,5\) However, there are few studies about factors...
associated with steroid-free remission in IIM patients.

Anthropometric measures are widely used as indicators of health outcomes. Higher body mass index (BMI) values are associated with an increased risk of death from cardiovascular disease. Further, waist circumference (WC), which indicates abdominal fat mass, predicts a higher mortality risk than BMI. Even with a normal BMI, an increase in WC is associated with an increase in mortality. Anthropometric measures such as obesity are beneficial for mortality or clinical outcomes. In rheumatoid arthritis (RA), a higher WC was associated with a higher health assessment questionnaire score and a lower incidence of remission; likewise, another study reported that a higher WC was associated with less disease severity at baseline and a better treatment response.

Height is also associated with health outcomes. Increased height in women is associated with a higher risk of cancer and death from cancer, but other studies reported that a shorter height was associated with a higher risk of cardiovascular disease or diabetes mellitus and severe disease activity and functional impairment in RA.

However, no studies have evaluated the association between anthropometric measures and treatment outcomes in IIM patients. Thus, we investigated the various clinical factors, including body measurements, that affect treatment outcome, that is, steroid-free remission in IIM.

Materials and methods

Study population

In this retrospective cohort study, we reviewed the electronic medical records of patients who were newly diagnosed with polymyositis (PM) or dermatomyositis (DM) and who had undergone an abdominal computed tomography (CT) scan between January 2000 and April 2018 at a tertiary referral hospital in Seoul, South Korea. IIM was diagnosed based on the fulfillment of three out of four of Bohan and Peter’s criteria. To identify patients with idiopathic inflammatory myositis meeting the inclusion criteria, we first searched the electronic medical records database for all those diagnosed with inflammatory myositis (ICD-10 codes of M33.x or M36.0) at our hospital and reviewed the patient records to confirm their eligibility. Included patients also met the 2017 EULAR/ACR classification criteria for adult and juvenile idiopathic inflammatory myopathies. Patients under 18 years of age at diagnosis were excluded. The index date was defined as the date of corticosteroid initiation after diagnostic work-up of IIM.

The following data were collected from the medical records at diagnosis: demographic information, including age and sex; body measurements, including weight, height and BMI; comorbid medical conditions such as hypertension, diabetes mellitus, interstitial lung disease based on high resolution CT finding with compatible pulmonary function test (PFT), renal insufficiency and malignancy; presence of dysphagia was confirmed by video fluoroscopic swallowing study indicating a severity greater than moderate; drug exposure, including corticosteroids and immunosuppressant within 1 month after diagnosis including methotrexate, azathioprine, calcineurin inhibitors, mycophenolate mofetil and cyclophosphamide; and laboratory data, including creatine kinase, myoglobin, lactate dehydrogenase, aldolase, erythrocyte sedimentation rate, C-reactive protein and autoantibodies (antinuclear antibody and anti-Jo-1 antibody). The study protocol was approved by the Institutional Review Board of Asan Medical Centre, Seoul, Korea (No. 2018-1770). The informed consent requirement was waived because of the retrospective design.

Assessment of WC

Baseline WC was measured from a single cross-sectional CT image that had been obtained within 3 months before or 1 month after diagnosis of IIM at the mid portion of the third lumbar spine. A value of estimated abdominal perimeter determined from CT scan is a valid measure of WC. After obtaining the cross-sectional image from the CT study, WC was automatically computed by applying image processing techniques using MATLAB software (MATLAB and Image Processing Toolbox R2018b, The MathWorks, Inc., Natick, MA, USA). First, the quality of the CT image was enhanced because the original image was not clear enough for automatic circumference computation. Then, to separate the object (i.e. the body part) from the background, we calculated a binary mask based on edge detection using a Sobel filter. Finally, WC was computed from the boundary of the mask.
**Definition of treatment outcome**

Steroid-free remission was defined as the discontinuation of corticosteroids for at least 3 months with clinical improvement including improvement of muscle power or skin rash, or stabilisation of PFT. The physicians’ decisions to discontinue corticosteroids were based on clinical improvement with gradual dose reduction without additional immuno-suppressants and biochemical disease activity results showing normalisation of creatine kinase levels. The cases of discontinuation of corticosteroids due to adverse event of corticosteroids, including steroid-induced myopathy or refractory to corticosteroids, were not considered as steroid-free remission.

**Statistical analysis**

The Chi-square and Fisher’s exact tests were applied to compare categorical data. Continuous variables were summarised by the mean (standard deviation) and analysed by Student’s t-test for parametric data and the Mann–Whitney U test for non-parametric data. The values from anthropometric measurements, including height, weight, BMI and WC, were divided into quartiles. Height and weight were also divided into sex-specific quartiles. The Cox proportional hazard model was applied to identify the factors associated with steroid-free remission, and the hazard ratios (HRs) and 95% confidence intervals (CIs) were reported. The values used for height, weight, BMI and WC were those measured at diagnosis. Variables that had a p-value of <0.2 in the univariate analyses and variables considered clinically important for the treatment outcome were selected for the multivariable analysis; otherwise, a p-value of <0.05 was considered statistically significant in all analyses. Variables in the multivariable analysis were further selected by backward stepwise regression, and those with significant p-values remained in the final model. We used R (Version 3.5.1, The R Foundation for Statistical Computing, Vienna, Austria) for all statistical analyses.

**Results**

**Comparison of clinical features according to steroid-free remission**

Of the 172 patients with IIM who met the Bohan and Peter’s criteria, 106 patients were included; 66 patients were excluded because of not having an abdominal CT scan. Abdominal CT scans were performed in the early stage of IIM between 3 months before or 1 month after diagnosis. Of the 106 IIM patients 70 had DM and 36 had PM, and the median follow-up duration was 35 months (range 0–178). All included patients met the 2017 EULAR/ACR classification criteria (definite, 92; probable, 14). Most patients were identified in rheumatology clinics (83%, 88/106) and the rest were identified in neurology clinics (17%, 18/106). Table 1 shows the baseline clinical characteristics and laboratory data for all patients. Overall, 67% (71/106) of the patients were female. The mean age at diagnosis was 54.6 ± 14.2 years, and the mean symptom duration was 5.3 ± 11.6 months.

Regarding body measurements, the mean weight, height, BMI and WC values were 57.6 ± 11.0 cm, 159.7 ± 8.5 cm, 22.5 ± 3.6 kg/m² and 81.1 ± 10.3 cm, respectively. During the follow-up periods, 35 patients achieved steroid-free remission; the median time to steroid-free remission was 17.3 months (range 4–80). There were no significant differences in the clinical features between the steroid-free remission group and the group that did not enter remission, but the frequency of cancer was lower in steroid-free remission patients than in those without remission (2.9% (1/35) versus 22.5% (16/71), p = 0.021). The proportion of immunosuppressant use within 1 month after diagnosis was higher in steroid-free remission patients than in those without remission (40.0% (14/35) versus 18.3% (13/71), p = 0.030). Thirty-eight patients were lost to follow-up, including 11 who died during the study period. Among 35 patients who achieved steroid-free remission, 22 patients had retained steroid-free remission status during follow-up periods. The median duration of steroid-free remission status was 22 months (range 3–167).

**Clinical factors associated with steroid-free remission in idiopathic inflammatory myositis patients**

In the cumulative event curve, the proportion of patients who achieved steroid-free remission within 5 years of treatment was significantly higher in patients who used an immunosuppressant within 1 month after diagnosis than in those who did not (Figure 1(a)). Further, the proportion of patients achieving steroid-free remission was higher in those with DM than in those with PM (Figure 1(b)). Interestingly, when stratified by WC, the proportion was the highest in the third quartile and the lowest in the fourth quartile (Figure 1(d)). For height, the proportion was the highest in the second and third sex-specific quartiles but the lowest in the fourth sex-specific quartile (Figure 1(d)).
Table 1. Baseline characteristics of patients with inflammatory myopathies.

| Sex               | Steroid-free remission |
|-------------------|------------------------|
|                   | All (n=106) | Male (n=35) | Female (n=71) | p     | No (n=71) | Yes (n=35) | p     |
| Sex, female       |            |             |               |       | 45 (63.4%) | 26 (74.3%) | 0.366 |
| Age at diagnosis (years) | 54.6 ± 14.2 | 57.6 ± 13.2 | 53.2 ± 14.6 | 0.134 | 56.4 ± 13.7 | 51.0 ± 14.8 | 0.066 |
| Follow-up duration (months) | 43.4 ± 42.5 | 40.3 ± 45.1 | 44.9 ± 41.3 | 0.333 | 29.5 ± 36.2 | 71.5 ± 40.6 | <0.001 |
| Symptom duration, months | 5.3 ± 11.6 | 3.2 ± 6.4 | 6.3 ± 13.3 | 0.226 | 5.5 ± 12.9 | 5.0 ± 8.7 | 0.173 |
| Myositis type     |            |             |               |       |           |           |       |
| Dermatomyositis   | 70 (66.0%) | 22 (62.9%) | 48 (67.6%) | 0.789 | 43 (60.6%) | 27 (77.1%) | 0.140 |
| Polymyositis      | 36 (34.0%) | 13 (37.1%) | 23 (32.4%) |       | 28 (39.4%) | 8 (22.9%) |       |
| Weight (kg)       | 57.6 ± 11.0 | 65.3 ± 11.2 | 53.9 ± 8.8 | <0.001 | 57.7 ± 11.0 | 57.6 ± 11.1 | 0.963 |
| Height (cm)       | 159.7 ± 8.5 | 168.0 ± 5.8 | 155.6 ± 6.3 | <0.001 | 160.5 ± 8.7 | 158.1 ± 7.8 | 0.156 |
| Body mass index (kg/m²) | 22.5 ± 3.6 | 23.1 ± 3.6 | 22.3 ± 3.7 | 0.295 | 22.3 ± 3.7 | 23.0 ± 3.5 | 0.404 |
| Waist circumference (cm) | 81.1 ± 10.3 | 83.5 ± 12.8 | 79.8 ± 8.6 | 0.132 | 81.5 ± 11.0 | 80.2 ± 8.7 | 0.571 |
| Comorbid conditions |          |             |               |       |           |           |       |
| Diabetes mellitus | 16 (15.1%) | 8 (22.9%) | 8 (11.3%) | 0.201 | 13 (18.3%) | 3 (8.6%) | 0.304 |
| Hypertension      | 35 (33.0%) | 15 (42.9%) | 20 (28.2%) | 0.196 | 27 (38.0%) | 8 (22.9%) | 0.179 |
| Interstitial lung disease | 35 (33.0%) | 11 (31.4%) | 24 (33.8%) | 0.980 | 23 (32.4%) | 12 (34.3%) | 1.000 |
| Cancer            | 17 (16%) | 5 (14.3%) | 12 (16.9%) | 0.949 | 16 (22.5%) | 1 (2.9%) | 0.021 |
| Dysphagia         | 24 (22.6%) | 14 (40.0%) | 10 (14.1%) | 0.006 | 19 (26.8%) | 5 (14.3%) | 0.232 |
| Medications       |          |             |               |       |           |           |       |
| Initial dose of prednisolone (equivalent) (mg) | 85.9 ± 122.2 | 98.3 ± 133.7 | 79.7 ± 116.6 | 0.006 | 74.8 ± 96.5 | 108.3 ± 161.6 | 0.455 |
| Immunosuppressant use within one month | 27 (25.5%) | 9 (25.7%) | 18 (25.4%) | 1.000 | 13 (18.3%) | 14 (40.0%) | 0.030 |

(Continued)
Table 1. (Continued)

| Muscle enzyme (IU/L) | Sex | Steroid-free remission |
|----------------------|-----|------------------------|
|                      | All (n=106) | Male (n=35) | Female (n=71) | p | No (n=71) | Yes (n=35) | p |
| Creatine kinase      | 5788.8 ± 1985.9 | 11216.5 ± 3352.6 | 3113.1 ± 4861.4 | 0.002 | 7066.8 ± 24052.9 | 3196.1 ± 4072.8 | 0.470 |
| Myoglobin*, n=98     | 1502.9 ± 2244.7 | 2411.7 ± 2861.7 | 1020.0 ± 1669.1 | 0.001 | 1729.8 ± 2490.8 | 1034.8 ± 1556.5 | 0.140 |
| Lactate dehydrogenase*, n=105 | 671.8 ± 441.4 | 737.3 ± 386.1 | 639.1 ± 465.8 | 0.043 | 687.9 ± 461.5 | 639.8 ± 402.9 | 0.661 |
| Aldolase*, n=86      | 33.1 ± 50.2 | 39.6 ± 61.8 | 29.6 ± 42.9 | 0.101 | 37.8 ± 58.6 | 24.2 ± 27.2 | 0.257 |

Autoantibodies

|                      | Sex | Steroid-free remission |
|----------------------|-----|------------------------|
|                      | All (n=106) | Male (n=35) | Female (n=71) | p | No (n=71) | Yes (n=35) | p |
| Antinuclear antibody | 43 (40.6%) | 15 (42.9%) | 28 (29.4%) | 0.736 | 23 (32.4%) | 20 (57.1%) | 0.015 |
| Anti-Jo-1*, n=101   | 8 (7.9%) | 4 (12.1%) | 4 (5.9%) | 0.433 | 6 (9.1%) | 2 (5.7%) | 0.711 |
| ESR*, n=92 (mm/h)    | 44.9 ± 25.6 | 39.4 ± 25.0 | 47.3 ± 25.7 | 0.174 | 46.4 ± 26.8 | 41.9 ± 23.2 | 0.428 |
| CRP*, n=92 (mg/dL)   | 1.8 ± 2.9 | 2.7 ± 3.4 | 1.3 ± 2.4 | 0.036 | 2.0 ± 3.0 | 1.4 ± 2.5 | 0.339 |

Results expressed as the mean ± standard deviation or number (%).
*Missing value was excluded from analysis.
CRP, C-reactive protein; ESR, erythrocyte sedimentation rate
A Cox proportional hazard regression analysis was performed to evaluate the clinical factors associated with steroid-free remission (Table 2). The early initiation of immunosuppressant therapy within 1 month after the diagnosis of IIM was strongly associated with steroid-free remission (HR 6.21, 95% CI 2.61–14.74, \( p < 0.001 \)). However, PM rather than DM (HR 0.21, 95% CI 0.09–0.53, \( p = 0.001 \)) and the presence of dysphagia (HR 0.15, 95% CI 0.05–0.50, \( p = 0.002 \)) showed inverse associations with steroid-free remission. The fourth WC quartile was associated with a lower rate of steroid-free remission compared with the first quartile (HR 0.24, 95% CI 0.07–0.85, \( p = 0.027 \)). Further, the second (HR 3.65, 95% CI 1.40–9.51, \( p = 0.008 \)) and third (HR 2.88, 95% CI 1.13–7.32, \( p = 0.027 \)) sex-specific height quartiles were more positively associated with steroid-free remission than the first sex-specific height quartile. To evaluate the association between the single anthropometric measurement and steroid-free remission, model 2 was adjusted for WC and model 3 was adjusted for sex-specific height. For WC, the third quartile showed a positive association with steroid-free remission (HR 2.74, 95% CI 1.08–6.92, \( p = 0.033 \)). However, the
fourth quartile showed an inverse association (HR 0.25, 95% CI 0.07–0.87, \( p=0.029 \)). For sex-specific height, the second and third quartiles were associated with steroid-free remission when first quartile was used as reference. However, the fourth quartile tended to display an inverse association with steroid-free remission.

**Discussion**

We showed that immunosuppressant use within 1 month after diagnosis was an important prognostic factor for the achievement of steroid-free remission, but PM and dysphagia were associated with a lower rate of steroid-free remission. Further, amongst anthropometric measurements, WC quartiles and sex-specific height quartiles were significantly associated with steroid-free remission.

Limited studies have investigated the treatment outcomes of initial combination therapy with corticosteroids and immunosuppressive agents. The azathioprine and corticosteroids combination was associated with better functional ability than corticosteroids alone. Further, treatment with methotrexate in addition to corticosteroids showed long-term survival benefits and facilitated
steroid tapering. Although a steroid-sparing immunosuppressive agent is generally initiated with corticosteroid treatment to reduce the cumulative dose of prednisone, there are no standardised therapeutic guidelines for the treatment of IIM, particularly due to the lack of randomised controlled trials and the rarity of the disease. Therefore, our findings, which are based on real-world data, suggest that the early initiation of immunosuppressive therapy is related to steroid-free remission.

Increased WC, which reflects true adiposity more accurately than increased BMI, has been suggested as the best single indicator of cardiovascular risk factors. Moreover, WC is a better predictor of all-cause and cause-specific mortality than BMI. However, several studies have reported that a high body fat percentage is a predictor of good prognosis in coronary artery disease or acute lung injury patients. Further, WC showed a U-shaped association with cardiovascular outcomes, which indicated that mild to moderate obesity had a beneficial effect in patients who underwent a percutaneous coronary intervention. The fourth WC quartile was associated with a lower rate of steroid-free remission than the first quartile; moreover, the probability of steroid-free remission was the highest in the third WC quartile and the lowest in the fourth WC quartile. These findings suggest that mild or moderate central obesity is a good prognostic factor in IIM patients whereas severe central obesity is a poor prognostic factor.

The relationship between height and mortality or treatment outcomes is diverse. Some studies suggest that there is an inverse relationship between height and longevity. Further, increased height is associated with the risk of cancer and dying from cancer; this association is more prominent in females. However, a shorter height is known to be associated with a higher risk of cardiovascular disease or diabetes mellitus and worse disease activity and functional impairment of RA. Interestingly, a previous study showed that the middle height group displayed better treatment outcomes for colorectal cancer than the extreme height group. This association may be explained by the increased insulin-like growth factor-1 (IGF-1) concentration in taller patients. In our results, the second and third sex-specific height quartiles were associated with steroid-free remission when first quartile was used as reference, but the fourth quartile tended to display an inverse association with steroid-free remission. These results have a similar pattern to those for WC; a medium height was a good predictor of treatment outcomes, but the greatest height was associated with a lower rate of steroid-free remission. Possible mechanisms for this finding include the higher concentration of IGF-1 in taller patients, which might be associated with the treatment response in inflammatory disease, or the relatively insufficient immunosuppressant dosage in taller patients compared with the middle height group. Future studies are necessary to identify the mechanisms responsible for the association between height and treatment outcomes in IIM.

The present study has some limitations. First, because the study design was retrospective and performed in a single referral tertiary centre, the number of patients in the cohort was relatively small and the potential for confounding bias and selection bias toward severely ill patients cannot be excluded. In fact, a considerable number of patients with IIM (38%) were excluded from the study because of not having an abdominal CT scan initially. However, there were no differences between the excluded and included patients in baseline characteristics (age, sex, symptom duration, type of IIM and comorbidities such as diabetes mellitus, interstitial lung disease and cancer). Thus, the probability of selection bias might be low. Second, diverse clinical variables such as muscle power and the change of anthropometric measurements that are easily measurable in routine clinical practice on treatment outcomes in IIM patients.

To the best of our knowledge, this is the first study showing the prognostic factors for steroid-free remission, which is very important for the long-term outcomes of patients with chronic inflammatory diseases. The findings also highlight the additional prognostic value of some body measurements that are easily measurable in routine clinical practice on treatment outcomes in IIM patients.

Our results suggest that the early initiation of immunosuppressant therapy, type of myositis and presence of dysphagia are strong predictors of steroid-free remission in IIM. Moreover, measurements of height and WC at baseline may provide an additional prognostic value for treatment outcomes.
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Conflict of interest statement
The authors declare that there is no conflict of interest.

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