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Thrombocytosis as a prognostic factor in polymyalgia rheumatica: characteristics determined from cluster analysis

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Abstract

Background: This study aimed to identify the clinical subgroups of polymyalgia rheumatica (PMR) using cluster analysis and compare the outcomes among the identified subgroups.

Methods: We enrolled patients with PMR who were diagnosed at Okayama University Hospital, Japan between 2006 and 2017, met the 2012 European League Against Rheumatism/American College of Rheumatology provisional classification criteria for PMR, and were treated with glucocorticoids. Hierarchical cluster analysis using variables selected by principal component analysis was performed to identify the clusters. Subsequently, the outcomes among the identified clusters were compared in the study. The primary outcome was treatment response at 1 month after commencement of treatment. The secondary outcome was refractory clinical course, which was defined as the requirement of additional treatments or relapse during a 2-year observational period.

Results: A total of 61 consecutive patients with PMR were enrolled in the study. Their mean age was 71 years, and 67% were female. Hierarchical cluster analysis revealed three distinct subgroups: cluster 1 ($n = 14$) was characterized by patients with thrombocytosis (all patients showed a platelet count of $>45 \times 10^4/\mu l$), cluster 2 ($n = 38$), by patients without peripheral arthritis, and cluster 3 ($n = 9$), by patients with peripheral arthritis. The patients in cluster 1 achieved treatment response less frequently than those in cluster 2 (14% *versus* 47%, $p = 0.030$). Refractory cases were more frequent in cluster 1 than in cluster 2; however, no significant difference was noted (71% *versus* 42%, $p = 0.06$).

Conclusions: Thrombocytosis could predict the clinical course in patients with PMR.

Keywords: cluster analysis, peripheral arthritis, polymyalgia rheumatica, prognostic factors, thrombocytosis

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Introduction

Polymyalgia rheumatica (PMR) is a relatively common inflammatory rheumatic syndrome that predominantly affects elderly people and causes shoulder and pelvic girdle pain.[1] The incidence of PMR increases with age in both sexes until 80 years, and the annual incidence of polymyalgia rheumatica in individuals older than 50 years was reported to be 10–60 cases per 100,000 people.[1] Its etiology is poorly understood; however, genetic factors, including human leukocyte antigen[2] and virus infections,[3] are considered to be contributing factors for the onset of PMR. Low doses of glucocorticoids (GCs) usually result in rapid improvement of symptoms; however, relapses occur in 30–50% of the patients with PMR[4–6] and GC treatment is often required for more than 5 years.[6,7] Approximately 20–30% of the patients diagnosed with PMR were finally diagnosed with rheumatoid arthritis (RA).[8,9] Although methotrexate (MTX) is used for refractory cases for a long period of time, the efficacy of using the anti-interleukin

(IL)-6 receptor tocilizumab (TCZ) is reported recently.[10,11] However, the indication of TCZ for patients with PMR has not been clarified.

Even though shoulder pain generally occurs in almost all patients with PMR, hip girdle involvement occurs in 50–90% of these patients;[12,13] peripheral arthritis in 15–40%;[5,12,13] and other symptoms, such as fever, fatigue, and weight loss, in 20–50%.[5,12,13] Previous reports showed several risk factors for poor prognosis in patients with PMR, such as peripheral arthritis, high acuter phase reactants, and treatment response;[14] however, the risk factors differed among the reports and those differences might relate to the different clinical designs.[14] For example, some inclusion criteria are difficult to exclude patients with RA,[15,16] and RA-like symptoms such as peripheral arthritis might be identified as a poor prognostic factor. Another study reports that treatment response to GC therapy was associated with poor outcomes,[5] but treatment response is the main factor for confirming the diagnosis of PMR clinically. Recently, the 2012 European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) provisional classification criteria for PMR have been proposed for standardized clinical research, especially focused on differentiating PMR from RA.[10] Also, the initial process includes evaluation of the criteria using the population with different treatment responses to initial GC.[12] Therefore, these criteria may reveal the relevant prognostic factors of PMR.

Cluster analysis is a statistical analysis that divides objects into clusters based on their characteristics. It is useful in studies involving heterogeneous diseases, especially those without existing candidate variables. Previous studies that employed cluster analysis exhibited relevant clinical variables in patients with RA,[17,18] systemic sclerosis,[19] and polymyositis/dermatomyositis.[20]

The purpose of this study was to identify the clinical subgroups of PMR classified under the 2012 EULAR/ACR criteria using cluster analysis and explore clinically relevant variables.

Methods

Patient selection

In this study, we enrolled outpatients and inpatients with PMR who were diagnosed at Okayama University Hospital, Japan between July 2006 and June 2017, met the 2012 EULAR/ACR provisional classification criteria for PMR, and were treated with GCs. Exclusion criteria were: (1) fulfillment of the 2010 ACR/EULAR classification criteria for RA, (2) complications with other rheumatic disorders, (3) newly diagnosed with cancer within 2 years, and (4) fulfillment of the 1990 ACR classification criteria for giant cell arteritis (GCA).[21]

This study was conducted according to the guidelines of the Declaration of Helsinki and the Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan. The study protocol was approved by the ethics committees of Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences (authorization number: Ken 1709-021). Patient consent was obtained by filling an opt-out consent form.

Data collection

Patient characteristics at the start of the treatment were reviewed for the following data: age, sex, body mass index, scores and items of the EULAR/ACR criteria for PMR and ACR/EULAR criteria for RA, clinical symptoms including arthralgia and myalgia, laboratory data, and treatment status. For treatment status, we collected the data on the dosage of GCs and whether disease-modifying antirheumatic drugs (DMARDs) and biological agents were used concomitantly during the observational period. C-reactive protein (CRP) levels at 1 week after the initiation of treatment were also collected.

Outcomes

The primary outcome of this study was treatment response within 1 month after commencement of the treatment. Treatment response was defined as the absence of PMR symptoms and normalization of the erythrocyte sedimentation rate (ESR) or CRP level. The secondary outcome was a refractory clinical course, which was defined as the requirement for additional treatment or relapse regardless of GC dosage during the 2-year observational period. Additional treatment included increased dose of GCs and concomitant use of DMARDs, such as MTX, and biological agents. Moreover, relapse was defined as a flare-up of PMR symptoms and positive conversion of ESR or CRP.

Statistical analysis

We initially decided on six variables for the cluster analysis, based on the sample size of this study.[22] Of the principal components with ⩾1 eigenvalue converted using principal component analysis (PCA), six principal components were selected in descending order of the eigenvalue. The variable with the highest loading value in each principal component was selected for cluster analysis. Continuous variables were categorized based on the upper or lower quartile. Hierarchical cluster analysis (Ward's method) was performed using the six variables selected in the PCA.

Clinical characteristics are presented as the mean ± standard deviation (SD) for continuous variables and patient number (percentage) for categorical variables. Decision coefficients were also calculated to evaluate the strength of the correlation between continuous variables. Patient characteristics and outcomes were compared among clusters using a one-way analysis of variance for continuous variables and Pearson's Chi-squared tests for categorical variables. The tests were two-tailed, and p values <0.05 were considered statistically significant. All statistical analyses were performed using the JMP for Windows software program, version 12.2.0 (SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics

A total of 61 consecutive patients with PMR were enrolled in the study. Their mean ± SD age was 71 ± 7 years, and 41 (67%) of the patients were female. None of the enrolled patients was positive for rheumatoid factor or anticyclic citrullinated peptide antibodies. However, morning stiffness was found in 52 patients (85%), hip pain in 55 (90%), peripheral arthritis in 13 (21%), and fever in 7 (11%). Only one patient was classified under the EULAR/ACR criteria for PMR with ultrasonography (US), whereas the other patients were classified according to those without US. The mean ± SD initial dosage of prednisolone was 13 ± 3 mg/day (0.25 mg/day/kg). There was no patient who could discontinue GCs without relapse in observational periods.

Of the enrolled patients, 38 (62%) of them failed to achieve treatment response within 1 month. During the mean ± SD observational period of 21 ± 6 months including the 13 (21%) patients who had been followed for less than 24 months, 30 patients (49%) required additional treatments or experienced relapses regardless of the glucocorticoids use at the point. Additional treatments included increasing the prednisolone dose in 11 patients (18%), concomitant use of MTX in 19 (32%), and concomitant use of sulfasalazine in two (3%).

Cluster analysis

The following variables on the patients' clinical characteristics before the treatment were used for PCA as candidate variables: age, sex, scores of the EULAR/ACR criteria for PMR and ACR/EULAR criteria for RA, morning stiffness, fever, white blood cell and platelet count, hemoglobin, ESR, CRP and albumin levels, and estimated glomerular filtration rate (eGFR).

The first to sixth components selected by PCA together explained 65% of the total variance. The following variables with the highest loading value on each component were selected for the cluster analysis: morning stiffness in component 1, scores of ACR/EULAR criteria for RA in component 2, eGFR in component 3, platelet counts in component 4, morning stiffness in component 5, and hip pain in component 6. Of these five variables (morning stiffness duplicated in components 1 and 5), three continuous variables were changed into categorical variables using quartiles. Hierarchical cluster analysis using these five categorical variables identified the final three distinct clusters (Figure 1).

The characteristics among the three clusters are shown in Table 1. All patients in cluster 1 had a platelet count of $>45 \times 10^4/\mu l$. This cut-off value was used as the definition of 'thrombocytosis' in previous studies,[23,24] therefore cluster 1 ($n = 14$) was characterized by thrombocytosis. There was no significant difference in CRP levels among three clusters and no correlation between platelet counts and CRP levels was found ($p = 0.95$). No significant differences were noted in the other characteristics of patients in clusters 2 and 3. Cluster 2 ($n = 38$) was categorized as PMR without peripheral manifestations. Among the 38 patients in cluster 2, 26 (68%) of them exhibited a EULAR/ACR criteria score of ⩾5 for PMR and none of the patients had peripheral arthritis. Cluster 3 ($n = 9$) was categorized as PMR with peripheral arthritis. All patients in this cluster had peripheral arthritis and had ACR/EULAR

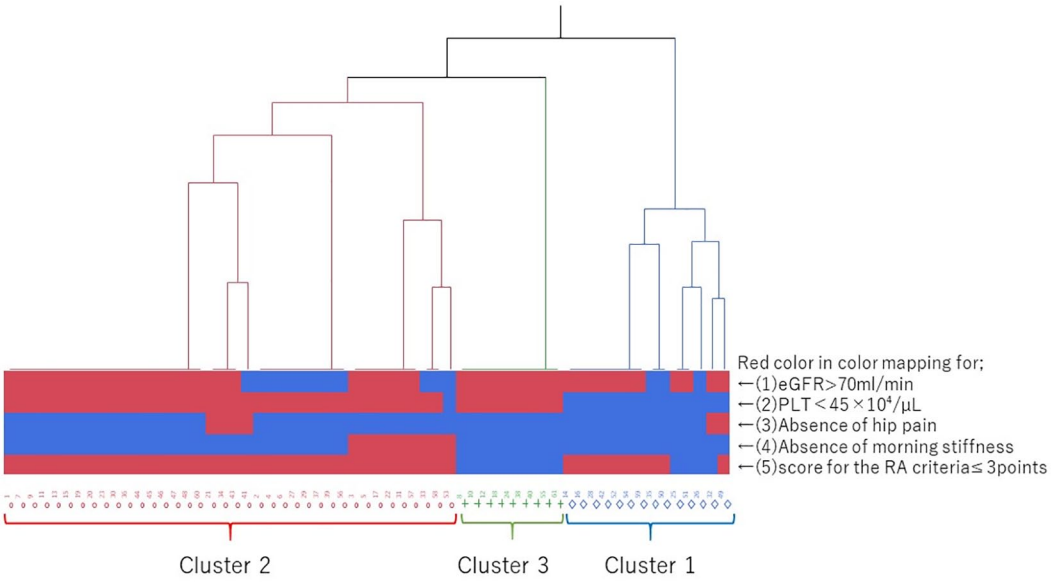

Figure 1. Dendrogram of a hierarchical cluster analysis with color map.
The dendrogram was obtained from 61 patients with polymyalgia rheumatica grouped into three clusters. The color map shows the patient and cluster characteristics with the variables selected using principal component analysis.
eGFR, estimated glomerular filtration; PLT, platelet; RA criteria, the 2010 American College of Rheumatology/ European League Against Rheumatism (EULAR) classification criteria for rheumatoid arthritis (RA).

classification criteria scores ⩾4 for RA. None of the patients in cluster 3 had fever or an ESR > 120 mm/h.

Patients in cluster 1 showed treatment response significantly less frequently than those in cluster 2 (14%, 47%, and 33% in clusters 1, 2, and 3, respectively; cluster 1 *versus* cluster 2, $p=0.030$; cluster 1 *versus* cluster 3, $p=0.28$). The refractory cases were more common in cluster 1 than in clusters 2 and 3; however, no significant difference was observed (71% in cluster 1, 42% in cluster 2, and 56% in cluster 3; cluster 1 *versus* cluster 2, $p=0.06$; cluster 1 *versus* cluster 3, $p=0.44$). The proportions of patients with concomitant use of MTX in clusters 1, 2, and 3 were 57%, 21%, and 33%, respectively (cluster 1 *versus* cluster 2, $p=0.012$; cluster 1 *versus* cluster 3, $p=0.26$). The CRP level was ⩾0.5 mg/dl; in 42% of cluster 1, 65% of cluster 2, and 63% of cluster 3 at 1 week after the initiation of treatment.

Discussion

In the present study, three clusters of patients with PMR were identified using the hierarchical cluster analysis. Cluster 1 included patients with thrombocytosis, cluster 2 included patients with peripheral arthritis, and cluster 3 included those without peripheral arthritis. The patients in cluster 1 exhibited poorer outcomes than those in cluster 2.

Thrombocytosis at baseline might be a good predictor of treatment response in patients with PMR. Secondary thrombocytosis is observed in several underlying conditions such as infection, tissue damage, chronic inflammatory disorders, and malignancy.[25] Platelet production is activated by thrombopoietin, also known as megakaryocyte growth and development factor, which is stimulated by inflammatory cytokines, especially IL-6.[26] A higher platelet count is suggested as a predictive factor of a good response to the treatment with TCZ in patients with RA.[27,28] Although MTX has been the first additional treatment option for refractory PMR cases, a recent report also showed the efficacy of TCZ for PMR.[1] As patients with PMR generally showed a quick response to GCs, the patients who should be treated with TCZ have not been identified. It should be elucidated whether thrombocytosis in PMR is appropriate indicator for TCZ treatment in a future study.

Patients without thrombocytosis were further divided into two clusters, according to whether they had peripheral arthritis, but the outcomes were comparable. Patients with peripheral arthritis has been seen as a distinctive group in PMR

Table 1. Clinical characteristics of the three clusters identified by clustering with variable selection based on principal component analysis.

	Cluster 1 ($n=14$): with thrombocytosis	Cluster 2 ($n=38$): without peripheral arthritis	Cluster 3 ($n=9$): with peripheral arthritis	*p* value
Age, years	68.1 ± 1.8	71.5 ± 1.1	70.3 ± 2.3	0.30
Female sex, *n* (%)	7 (50)	28 (74)	6 (67)	0.27
PMR criteria score, points	5.1 ± 0.2	5.1 ± 0.1	5.0 ± 0.3	0.89
RA criteria score, points	3.2 ± 0.1	2.9 ± 0.1	4.2 ± 0.2	<0.0001
Morning stiffness, *n* (%)	14 (100)	29 (77)	9 (100)	0.041
Fever (>38°C), *n* (%)	1 (7)	6 (16)	0 (0)	0.32
Hip pain, *n* (%)	12 (86)	34 (89)	9 (100)	0.51
Peripheral arthritis, *n* (%)	4 (29)	0 (0)	9 (100)	<0.0001
WBCs, /μl	9797 ± 632	7934 ± 384	9589 ± 789	0.021
Hb, g/dl	11.9 ± 0.4	11.2 ± 0.3	11.9 ± 0.5	0.25
PLT $\times 10^4$/μl	54.1 ± 2.3	35.7 ± 1.4	33.9 ± 2.8	<0.0001
ESR > 120 mm/h, *n* (%)	3 (21)	11 (30)	0 (0)	0.16
CRP, mg/dl	6.6 ± 1.1	6.2 ± 0.7	5.6 ± 1.3	0.85
Alb, g/dl	3.1 ± 0.1	3.4 ± 0.1	3.3 ± 0.2	0.21
eGFR, ml/min/1.73 m²	85.7 ± 4.7	76.2 ± 2.9	88.4 ± 5.9	0.08

Data are presented as mean ± standard deviation and patient number (percentage). PMR criteria, the 2012 European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) classification criteria for polymyalgia rheumatica (PMR) without ultrasonography; RA criteria, the 2010 ACR/EULAR classification criteria for rheumatoid arthritis (RA).
Alb, albumin; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; ESR, erythrocyte sedimentation rate; Hb, hemoglobin; PLT, platelet; WBC, white blood cell.

since PMR patients are often diagnosed with RA finally.[8,9] The 2012 EULAR/ACR provisional criteria for PMR were expected to make a differential diagnosis, especially from RA;[15] however, a recent report showed the difficulty indistinguishing PMR from RA using the EULAR/ACR criteria.[29] In the present study, patients with peripheral arthritis emerged as one of the characteristic clusters. As these patients showed higher ACR/EULAR classification criteria scores for RA, it might still be difficult to exclude RA using the EULAR/ACR criteria for PMR; however, no significant difference was noted in the remission rate and refractory outcome between patients with and without peripheral arthritis under daily clinical practice. Moreover, a previous report showed that peripheral manifestations in PMR were not associated with refractory outcomes.[30] Therefore, these criteria could differentiate patients with RA with different prognoses from patients with PMR.

In the present study, a treatment response at 4 weeks was achieved in only 38% of the patients. Generally, patients with PMR respond rapidly to initial GC therapy and show symptomatic improvement within approximately 5 days.[31] In a prospective cohort study conducted to develop the EULAR/ACR criteria for PMR, the results showed that 73% of the patients improved at 4 weeks.[12] However, only half of those patients achieved a complete response with normalizations of ESR or CRP.[32] Since 70% of the patients

in the present study had no symptoms at 4 weeks, the rates of treatment response to GCs might differ, based on the definition of treatment response. In addition, more severe patients might be included in this study because our institution is a referral hospital. On the other hand, refractory patients are comparable with the previous reports;[4,5] however, all patients continued GCs, therefore refractory case might increase in longer observation.

This study has limitations. First, US was performed in only 10 cases. Since the specificity and sensitivity rates were higher in the criteria with US than that without US based on the EULAR/ACR criteria for PMR,[15] other diseases, such as RA, might have been included and may have affected the cluster analysis; however, this limitation might not have seriously affected our results because peripheral arthritis as an RA-like symptom was not related to the outcomes. In addition, some patients with GCA might have been included because the imaging test for the diagnosis of GCA was not performed in all patients. Second, validation analysis could not be performed because of small sample, so our results have to be validated in a future study. Third, the mean starting dose at 13 mg of prednisolone is low compared with the recommended dosage range (12.5–25 mg);[33] however, one report suggested the adequate prednisolone dosage is related to body weight,[34] in which their dosage was 0.19 mg/kg. The mean staring prednisolone dosage per weight in our study was 0.25 mg/kg and not overly low considering the body size in our Japanese patients.

In conclusion, the results of the study suggest that thrombocytosis could predict the clinical course in patients with PMR.

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Conflict of interest statement

The authors declare that there is no conflict of interest. We disclosed that Jun Wada received speaking honoraria from Astellas, Boehringer Ingelheim, Daiichi Novartis, Sankyo, and Tanabe Mitsubishi, and grant support from Astellas, Bayer, Baxter, Chugai, Daiichi Sankyo, Kissei, Kyowa Hakko Kirin, MSD, Novartis, Novo Nordisk, Ono, Otsuka, Pfizer, Teijin, Torii, and Takeda. K.S. has received lecture fee from Chugai. All other authors declare that they have no competing interests.

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