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Clinical Characteristics of Psoriasis for Initiation of Biologic Therapy: A Cluster Analysis

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Background: Psoriasis is a complex and heterogeneous disease that widely affects a patient's life. Biological therapy is usually prescribed in patients with severe psoriasis that do not respond to conventional treatment. However, data on the specific patient characteristics receiving biologics are still unavailable.
Objective: To classify patients with psoriasis into subgroups with distinct phenotypes through cluster analysis, and to evaluate the differences between the clusters to predict disease prognosis by examining the response to biological therapy.
Methods: The clinical characteristics of the patients with psoriasis were investigated and categorized using hierarchical cluster analysis. After clustering, the clinical characteristics of the patients were compared and the initiation of treatment with biologics according to the clusters were evaluated.
Results: A total of 361 patients with psoriasis were classified into two clusters using 16 distinct clinical phenotypes. Group 1 (n=202) consisted of male smokers and alcohol users with higher psoriasis area and severity index (PASI), older age of onset, higher body mass index, and comorbidities including psoriatic arthritis, hypertension, and diabetes when compared to group 2 (n=159). Group 1 had a significantly higher probability of biological treatment initiation than group 2 (p=0.039). The measured risk factors for the initiation of biologics compared were PASI (p<0.001) and nail involvement (p=0.022).
Conclusion: Cluster analysis classified patients with psoriasis into two subgroups according to their clinical characteristics. Predicting the disease prognosis using a combination of specific clinical parameters may aid in the management of the disease.

Keywords: Biological therapy, Cluster analysis, Psoriasis

INTRODUCTION

Psoriasis is a chronic immune-related inflammatory skin disorder that affects the lives of patients and increases the risk of various comorbidities[1]. The conventional treatment of psoriasis mainly consists of phototherapy or oral immunosuppressants, such as methotrexate (MTX) and cyclosporine. However, these modalities have shown varying responses among patients, and did not treat the disease in some patients; there are also concerns about associated systemic adverse events. The development of biologic therapy has led to the introduc-

tion of a new treatment strategy for psoriasis over the past two decades[2]. Biologic therapy showed better effects than oral immunosuppressants without serious systemic adverse events such as liver and kidney dysfunctions[3].

For the management of moderate-to-severe psoriasis, according to the National Health Insurance regulations in South Korea, biologics can be administered as medical insurance fees if there is no response even after 6 months of conventional treatment; therefore, most patients received conventional treatment over 6 months, and only patients who did not respond to conventional treatment were administered biologic

agents. Thus, it was assumed that the initiation of biologics might be associated with disease severity, poor disease prognosis, and unresponsiveness to conventional treatment. Greater severity of psoriasis is associated with poorer quality of life[4]. Additionally, the prevalence of major medical comorbidities increases with the severity of the disease[5]. Psoriasis is a complex, heterogeneous disease involving immunologic, genetic, and environmental factors; therefore, evaluating the risk factors for poor prognosis of the disease is challenging[6].

Cluster analysis is a machine-learning method used to categorize individuals into subgroups based on heterogeneous clinical data[7-9]. Unsupervised learning, including hierarchical clustering and *k*-means clustering, is an appropriate method for classification without prior knowledge[10]. This technique divides patients with psoriasis into subgroups using various clinical characteristics, allowing the identification of patient groups that are most associated with the initiation of biologics, corresponding to poor long-term outcomes and ineffectiveness of conventional treatment.

This study aimed to describe patients with psoriasis according to clusters of heterogeneous clinical data, identify a novel pattern of the initiation of biologics, and demonstrate the specific risk factors for the initiation of biologics.

MATERIALS AND METHODS

Study population
A retrospective study was conducted on patients diagnosed and treated for plaque psoriasis at Ajou University Hospital (Suwon, Republic of Korea) between 2017 and 2021. The diagnosis of plaque psoriasis was based on clinical manifestations and was confirmed by histopathology. Clinical and laboratory data were collected retrospectively through a review of medical records. Patients with insufficient baseline clinical data or those who discontinued follow-up were excluded. They were divided into a conventional treatment group and a biological treatment group. The conventional treatment group included patients in whom the disease was controlled with an oral immunosuppressant, including MTX and cyclosporine, and phototherapy during the entire follow-up period. The biologics treatment group included patients who started biologic therapy due to insufficiently controlled disease by conventional treatment during the entire follow-up period. The biologics included adalimumab, ustekinumab, secukinumab,

guselkumab, ixekizumab, and risankizumab. The data from the entire follow-up period of all patients and the period from the first day of the visit to the day of initiation of biologic treatment was collected. This study was approved by the Institutional Review Board of Ajou University Hospital (AJIRB-BMR-15-339). Informed consent was not required.

Clinical characteristics
The baseline data selected for analysis included the frequently observed demographics and baseline characteristics of the included patients[11,12]. Clinical and laboratory data were retrieved from the first visit medical record and all variables were required to be filled in the patient's record. The following variables were selected for cluster analysis: sex, psoriasis area and severity index (PASI), body surface area (BSA), age at onset, body mass index (BMI), family history of psoriasis, nail involvement, psoriatic arthritis, smoking, alcohol consumption, hypertension, and diabetes. Laboratory tests were performed at the first visit, and the following variables were included in the cluster analysis: white blood cell (WBC) count, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP).

Cluster analysis
Hierarchical cluster analysis was conducted to define subgroups of patients with similar characteristics[13]. It is a technique used to classify objects into optimally homogenous groups based on empirical measures of similarity[14]. Characteristics were weighted in order of their ability to minimize the intra-cluster and to maximize the inter-cluster distances using Gower's distance[15]. A complete linkage method with a high agglomeration coefficient was used, taking the longest distance between two points where each point belongs to each cluster from the pair of clusters[16]. In the dendrogram of the cluster analysis, the patients were divided into two clusters, and it was assumed that these two subgroups could reflect the most relevant and significant data on psoriasis (Fig. 1).

Statistical analysis
Clinical variables were presented as means with standard deviations (SDs) for continuous variables, and frequencies with percentages for categorical variables. Differences in clinical characteristics between clusters were compared using the Student's t-test or Wilcoxon rank-sum test for continuous variables and the chi-squared test or Fisher's exact test for
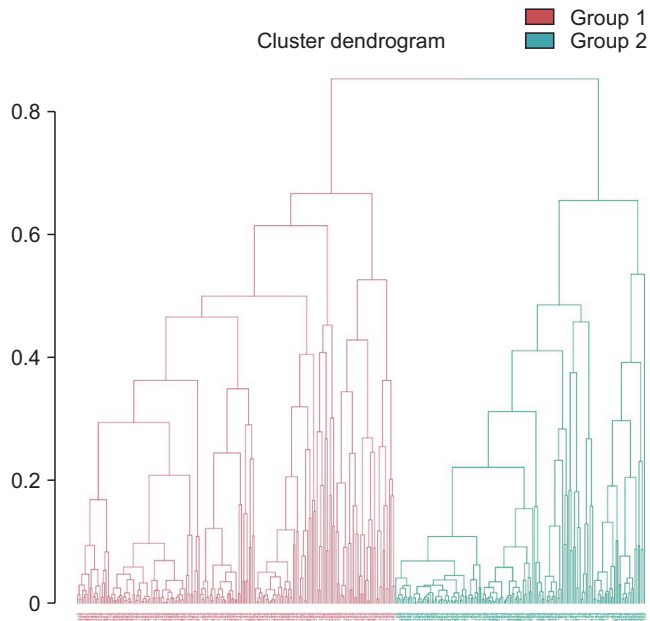
Fig. 1. Dendrogram from hierarchical cluster analysis of 361 patients and 16 comorbidities. Cluster analysis was performed using Gower's distance and complete linkage method.

categorical variables. Initiation of biological treatment with corresponding 95% confidence intervals (CIs) was estimated by Kaplan–Meier analysis and compared using a log-rank test. To evaluate the predictors of biological treatment initiation, clinically relevant variables were entered into a multivariable Cox proportional hazards regression model according to the clusters. All tests were two-sided, and p-values <0.05 was considered to be statistically significant. All statistical analyses were performed using R software (v. 4.1.0; The R Project for Statistical Computing, www.r-project.org).

RESULTS

This study included 434 patients with plaque psoriasis and sufficient clinical data were available for 361 patients. Enrolled patients showed male predominance (59.8%) with a mean age of 39.6 years (SD 14.1 years). All patients were naive to biologic therapy, and 80 (22.1%) were treated with biologics. The number of users for each biologic was as follows: adalimumab (16/80; 20.0%), ustekinumab (6/80; 7.5%), secukinumab (22/80; 27.5%), guselkumab (8/80; 10.0%), ixekizumab (3/80; 3.8%), and risankizumab (25/80; 31.3%). The mean follow-up period of all patients was 16.26 months (SD 16.19 months), and among the biologics treatment group, the mean period until

initiation of biologics was 12.45 months (SD 10.72 months). Table 1 shows the clinical characteristics of all patients.

Cluster analysis
Hierarchical clustering was performed to divide patients into subgroups. The analysis resulted in an optimal division of the sample into two clusters consisting of 202 and 159 patients. The clusters were labeled as groups 1 and 2 (Table 1). Group 1 consisted of male patients with, higher PASI, higher BSA, older age of onset, higher BMI, presence of a family history of psoriasis, nail involvement, psoriatic arthritis, smoking, alcohol consumption, hypertension, diabetes, higher WBC, normal ESR, and higher CRP levels than group 2 patients. The variables that significantly differed were sex, PASI, BSA, age of onset, BMI, smoking, alcohol consumption, hypertension, and diabetes. It was assumed that group 1 had a more severe form and associated comorbidities than group 2.

Risk of initiation of biologic therapy in each cluster
According to the National Health Insurance regulations in South Korea, biologic therapies for psoriasis are administered only if the disease is not sufficiently controlled with conventional treatment for over 6 months. Thus, the initiation of biologic treatment is a surrogate index of severe psoriasis and poor prognosis[12]. The cumulative incidence of biological treatment initiation using the Kaplan–Meier method was compared cluster-wise during the follow-up period (Fig. 2). Group 1 revealed a significantly higher probability of biological treatment initiation than group 2. Furthermore, the difference between clusters was significant according to the log-rank test for the entire follow-up period, with a gradual increase in patients receiving biological treatment ($p=0.039$). Thus, group 1 had a higher probability of initiation of biologics than group 2.

Moreover, a multivariate Cox proportional hazard regression model was performed to identify risk factors for the initiation of biologic therapy according to the groups by cluster analysis. Among the clinical variables, PASI, BMI, and nail involvement, which are clinically important factors for psoriasis, were included in the multivariable Cox proportional hazard regression model (Fig. 3). Multivariate analysis revealed that PASI (hazard ratio [HR], 1.08; 95% CI, 1.04~1.12; $p<0.001$) and nail involvement (HR, 1.71; 95% CI, 1.08~2.72; $p=0.022$) were significantly associated with group 1, which had a higher probability of initiation of biological treatment. The results

Table 1. Clinical characteristics of the study population and comparison of characteristics according to clusters

Characteristic	All patients (n=361)	Group 1 (n=202)	Group 2 (n=159)	p-value*
Sex				<0.001
Male	216 (59.8)	163 (80.7)	53 (33.3)	
Female	145 (40.2)	39 (19.3)	106 (66.7)	
PASI	9.19±5.78	10.06±6.28	8.08±4.87	0.003
BSA	13.91±10.41	15.30±11.23	12.14±9.01	0.005
Age of onset (yr)	26.15±12.79	30.19±12.89	26.30±12.91	0.002
BMI (kg/m^2)	24.12±3.98	24.70±3.92	23.37±3.94	<0.001
Family history of psoriasis	50 (13.9)	28 (13.9)	22 (13.8)	0.995
Nail involvement	103 (28.5)	65 (32.2)	38 (23.9)	0.084
Psoriatic arthritis	21 (5.8)	15 (7.4)	9 (5.7)	0.504
Smoking[†]	145 (40.2)	141 (69.8)	4 (2.5)	<0.001
Alcohol consumption[‡]	192 (53.2)	181 (89.6)	11 (6.9)	<0.001
Hypertension	24 (6.6)	20 (9.9)	4 (2.5)	0.005
Diabetes	13 (3.6)	11 (5.4)	2 (1.3)	0.034
WBC count				0.193
High	20 (5.5)	14 (6.9)	6 (3.8)	
ESR				0.089
High	21 (5.8)	8 (4.0)	13 (8.2)	
CRP				>0.999
High	10 (2.8)	6 (3.0)	4 (2.5)	
Treatment				0.009
Conventional treatment[§]	281 (77.8)	147 (72.8)	134 (84.3)	
Biologics treatment[‖]	80 (22.2)	55 (27.2)	25 (15.7)	
Follow-up period (mo)	16.26±16.19	12.61±12.97	12.11±13.57	0.197

Values are presented as number (%) or mean±standard deviation. PASI: psoriasis area and severity index, BSA: body surface area, BMI: body mass index, WBC: white blood cell, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, SD: standard deviation. *Differences in clinical characteristics between clusters were compared using the Student's t-test or Wilcoxon rank-sum test for continuous variables and the chi-square test or Fisher's exact test for categorical variables. [†]Included ex- and current smokers. [‡]Included ex- and current drinkers. [§]Conventional treatment includes oral immunosuppressant including methotrexate and cyclosporine and phototherapy. [‖]Biologics treatment was measured when treatment was initiated during the entire follow-up period and include adalimumab, ustekinumab, secukinumab, guselkumab, ixekizumab, and risankizumab.

revealed that among various characteristics, PASI and nail involvement were significantly associated with a high risk for the initiation of biologics in patients with psoriasis.

DISCUSSION

In this study, 361 patients with plaque psoriasis were divided into two subgroups in an unbiased manner using cluster analysis. The two groups revealed relevant clinical features. One group consisted of male smokers and alcohol users with high severity of disease and comorbidities such as psoriatic arthritis, hypertension, and diabetes. This group revealed a significantly higher probability of initiating biologics during the entire follow-up period, representing a clinical index of poor prognosis in psoriasis.

Psoriasis is associated with a variety of clinical features, comorbidities, and complex pathogenesis. Many studies have investigated the risk factors and comorbidities of psoriasis; however, the relationship between clinical characteristics and disease prognosis or treatment response has not yet been established[17]. One study in the U.K. and the Republic of Ireland compared the demographics and disease characteristics of patients with psoriasis between biologics and comparator control[12]. Limited clinical data exists regarding psoriasis in non-

Caucasian racial and ethnic groups[18]. In addition, hierarchical cluster analysis is an unsupervised machine-learning method without prior knowledge, with high specificity and a low mis-

classification rate[19]. In previous studies, cluster analysis was performed for patients with psoriasis primarily to measure the relationship between the disease and the quality of life. Such analysis for variable clinical features has rarely been reported[20,21]. To the best of our knowledge, this is the first cluster analysis performed in Asian patients to demonstrate psoriasis and related conditions with the initiation of biologics and reflects real-world data on the initiation of biologics for the disease. Although the data in the study are well-known among Caucasians, our results had a strength to confirm these results in Asians with a novel statistical approach.

Sixteen clinical parameters important for psoriasis were entered into cluster analysis and the patients were divided into two subgroups. Among the variables, sex, PASI, BSA, age of onset, BMI, smoking, alcohol consumption, hypertension, and diabetes were associated with significant differences between the two clusters.

Group 1 with male sex, higher BMI, smoking status, and alcohol use had a higher probability of initiation of biologics than that group 2. A previous study reported a higher risk for psoriasis in ex-smokers and current smokers than that in non-
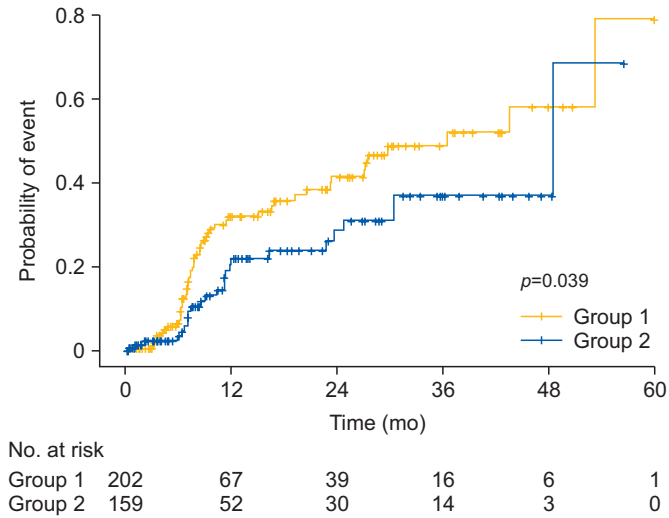
Fig. 2. Cumulative incidence of biologics initiation according to the cluster. The analysis was performed by the Kaplan–Meier analysis and compared by the log-rank test.
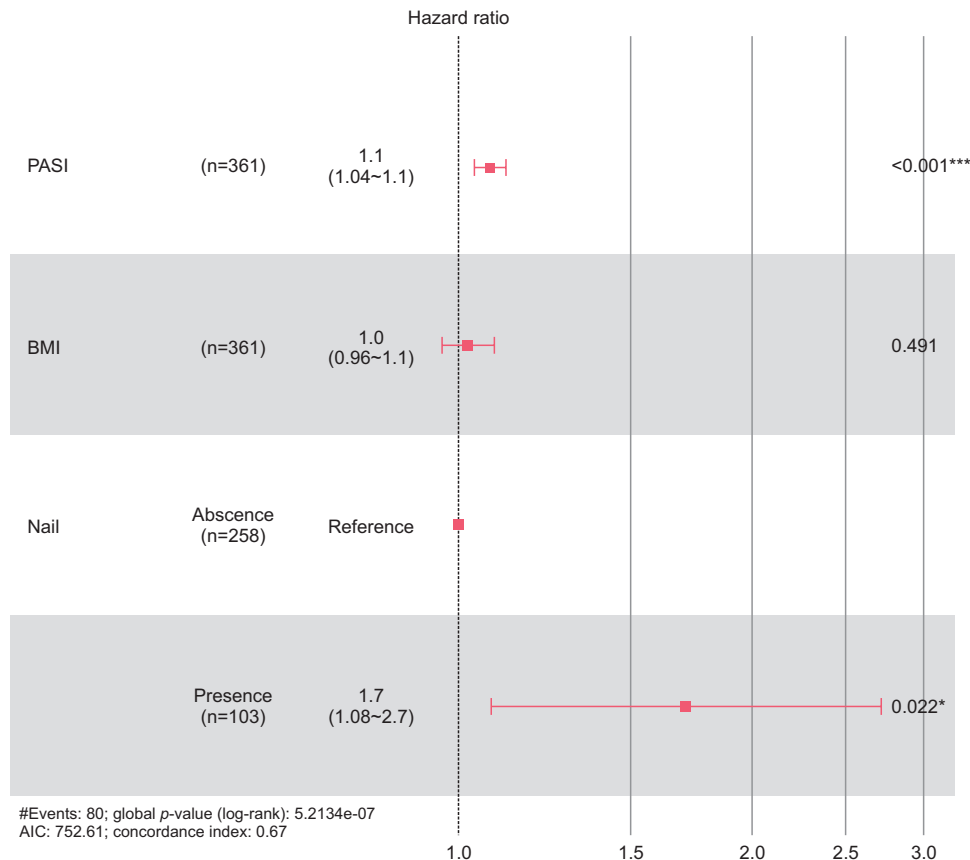
Fig. 3. Forest plots showing hazard ratios of biologics initiation in psoriasis. Hazard ratio by associated clinical variables using multivariable Cox proportional hazards regression model. PASI: psoriasis area and severity index, BMI: body mass index. Statistically significant (*$p<0.05$, ***$p<0.001$).

smokers; also, alcohol use was found to be associated with the disease in men[22]. Additionally, obese patients with a high BMI poorly responded to systemic treatment[23]. Furthermore, psoriasis is a risk factor for cardiovascular disease, and it can be driven by conditions such as smoking, alcohol consumption, and obesity[17]. These factors were found to be associated with poor prognosis and low treatment response to conventional treatment.

Group 1 presented higher PASI and BSA scores than group 2, indicating the severity of psoriasis. Our results showed that the higher the initial disease severity, the less responsive the patient was to conventional treatment, and the higher the probability of initiation of biologics. PASI is also related to the dermatology life quality index in patients with chronic moderate-to-severe plaque psoriasis, indicating a correlation between disease severity and psychological burden in psoriasis[24]. Altogether, higher initial PASI and BSA correlate with poor long-term outcomes and could affect the quality of life of affected patients.

Psoriasis has been classified according to the age of onset: early-onset psoriasis, onset before the age of 40 years; and late-onset psoriasis, onset at or after the age of 40 years[25]. These two classifications have different clinical and immunogenetic characteristics[25]. Patients with early-onset psoriasis are known to receive more biological therapy than those with late-onset psoriasis[26]. In our study, the age of onset ranged from 5 to 75 years old, and in both groups, most of the patients had early-onset psoriasis (30.19 [12.89] vs. 26.30 [12.91]). One study in Korea reported that early-onset psoriasis is related to a more extensive involvement of psoriasis than late-onset psoriasis cases[27]. Furthermore, a younger age of onset in patients was correlated with a high severity of PASI >10 (PASI <10, 39.3 [16.2]; PASI ≥10, 36.4 [17.0])[27]. In contrast, results of the current study showed that patients with older age of onset were more likely to initiate biologics. Further research is warranted on long-term prognosis according to age and early-onset psoriasis.

Data using a multivariate Cox regression model to determine the risk factors for the initiation of psoriasis regardless of clusters, found that PASI and nail involvement were the only significant risk factors. Nail involvement in psoriasis may be a sign of a more severe form of the disease or a precursor of psoriatic arthritis[28]. Psoriatic arthritis is related to a severe psoriasis phenotype and nail pitting[29]. Data of the present study suggests that, PASI and nail involvement, representing the severity of psoriasis, are related to the risk of initiation of biologic therapy in psoriasis. Furthermore, the result of nail involvement indicates that psoriatic arthritis might be an independent risk factor for the initiation of biologic therapy. Further investigations will be needed to evaluate the relationship between psoriatic arthritis and the initiation of biologics in psoriasis.

This study had certain limitations. First, data were collected retrospectively through a review of medical records. Due to the limitations of retrospective studies, there may be selection bias or insufficient clinical data. However, a specific form for patients with psoriasis in the electronic medical chart was used; thus, the probability of losing data was relatively low. Second, this was a single-center study leading to the risk of limited patient distribution and clinical data. Third, treatment before the initial day of the visit was not considered. Patients who have previously been treated are likely to have a low initial PASI despite higher severity; thus, the results regarding severity could be confused.

In conclusion, a hierarchical cluster analysis was performed to sub-classify patients with psoriasis based on clinical characteristics through machine-learning. Group 1 consisted of male smokers with higher BMI, alcohol use, higher PASI and BSA, older age of onset, presence of hypertension and diabetes, in combination with poor prognostic factors was associated with the initiation of biologics during the entire follow-up period. The heterogeneous characteristics of patients with psoriasis were classified, enabling physicians to predict poor prognostic factors and to consider the initiation of biologics in patients with these clinical phenotypes.

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CONFLICTS OF INTEREST

DATA SHARING STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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