Available online at www.medicinescience.org

ORIGINAL ARTICLE

Medicine Science International Medical Journal

Medicine Science 2025;14(3):870-6

Pigmentation traits and inflammatory arthritis: Associations between eye and skin color, diagnosis, and treatment patterns

Fatih Albayrak[1], Emrah Koc[2], Mustafa Berhuni[3], Gizem Gurbostan Soysal[4], Mehmet Gol[5]

[1]*Gaziantep University Faculty of Medicine, Department of Rheumatology, Gaziantep, Türkiye*
[2]*Adana City Hospital, Department of Rheumatology, Adana, Türkiye*
[3]*Gaziantep Islam Science and Technology University, Faculty of Medicine, Department of Ophthalmology, Gaziantep, Türkiye*
[4]*Health Sciences University, Gaziantep City Hospital, Department of Ophthalmology, Gaziantep, Türkiye*
[5]*Gaziantep Islam Science and Technology University, Faculty of Medicine, Department of Physiology, Gaziantep, Türkiye*

Received 14 July 2025; Accepted 04 August 2025
Available online 01 September 2025 with doi: 10.5455/medscience.2025.07.193

Abstract

The aesthetic features of pigmentation, specifically eye and skin color, show a significant correlation with the biological etiology of autoimmune diseases, challenging traditional views. The present study assessed the interplay between pigmentation traits and diagnostic classification, as well as treatment strategies, within a population of patients afflicted with rheumatoid arthritis (RA), spondyloarthritis (SpA). A cross-sectional retrospective analysis was conducted involving 215 patients diagnosed with RA, ankylosing spondylitis (AS), or psoriatic arthritis (PsA). Ocular and cutaneous pigmentation (brown, blue, green; light vs dark shades), were recorded alongside demographic, diagnostic, and therapeutic data. A structural equation model (SEM) was employed to evaluate the impact of pigmentation on diagnostic and treatment outcomes. Individuals with darker skin tones were significantly associated with SpA diagnoses (β=-0.344, $p<0.001$). A modest association was found between eye color and diagnosis (β=0.282, $p=0.037$), and eye color also influenced treatment assignment (β=0.300, $p=0.041$). Sex remained the most influential factor for treatment allocation among all variables examined (β=0.947, $p<0.001$). An association was observed between pigmentation traits and diagnostic groupings, but not treatment allocation, suggesting a possible connection to the underlying pathophysiology. This research warrants further investigation into the genetic and immunological connections between pigmentation and autoimmune diseases.

Keywords: Autoimmune rheumatic diseases, phenotypic characteristics, rheumatoid arthritis, spondyloarthritis, structural equation modeling

Introduction

The phenotypic expression of eye and skin pigmentation is a readily observable trait resulting from complex interactions of genetic, environmental, and ethnic influences. Although historically viewed as solely aesthetic characteristics, recent research indicates a correlation between these pigmentation patterns and systemic physiological processes, such as autoimmune and inflammatory diseases [1,2]. The concentration of melanin, the pigment responsible for skin and eye color, provides photoprotection and potentially reflects inherent genetic factors affecting disease susceptibility and progression [3-6].

Rheumatoid arthritis (RA), ankylosing spondylitis (AS), and psoriatic arthritis (PsA) constitute a subset of complex seronegative spondyloarthritis characterized by chronic inflammation and autoimmunity [7]. Despite a strong understanding of the genetic and immunopathological mechanisms, the influence of observable traits like eye and skin color on disease expression and clinical treatment warrants additional research. Considering the genetic determination of pigmentation, observed correlations with disease presentation likely reflect underlying genetic factors [8]. The potential influence of eye and skin color on autoimmune inflammatory diseases presents a promising avenue for future research.

Prior research has suggested correlations between pigmentation and systemic illness. Pleasants et al. observed a heightened prevalence of light-colored eyes among

CITATION
Albayrak F, Koc E, Berhun M, et al. Pigmentation traits and inflammatory arthritis: Associations between eye and skin color, diagnosis, and treatment patterns. Med Science. 2025;14(3):870-6.

Corresponding Author: Fatih Albayrak, Gaziantep University Faculty of Medicine, Department of Rheumatology, Gaziantep, Türkiye
Email: drfalbayrak@yahoo.com

DOI: 10.5455/medscience.2025.07.193

individuals with idiopathic pulmonary fibrosis, indicating a potential genetic predisposition shared between pigmentation and connective tissue pathologies [9]. Correspondingly, Hashemi et al. demonstrated a link between iris color and ocular anatomical traits, thereby implying the existence of potential immunological factors [10]. Furthermore, cancer biology research reveals a correlation between eye color and the likelihood of developing specific cancers linked to pigmentation, like uveal melanoma, highlighting the significance of melanin traits in overall biology [6].

Despite these research findings, the effect of pigmentation on clinical choices and diagnoses in autoimmune rheumatic diseases is still largely unknown. The potential for subconscious clinical bias and the genetic correlation with pigmentation suggests that understanding such associations may be crucial for advancements in personalized medicine.

The objective of this study is to analyze the distribution of eye and skin color in patients with RA, AS, and PsA, and to evaluate the potential influence of these traits on diagnostic processes and treatment decisions. This research seeks to expand the current understanding of the relationship between phenotypic diversity, autoimmune pathogenesis, and observable pigmentation variations in disease presentation and treatment.

Material and Methods

Study Design and Participants

This is a pilot study and we conducted a retrospective cross-sectional study to explore the links between pigmentation characteristics and clinical data among individuals with inflammatory rheumatic diseases. This study comprised 215 adult patients diagnosed with one of three arthritic conditions: RA (n=94), AS (n=89) or PsA (n=32). The research included patients who received their diagnosis based on the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for RA [11] the Assessment of SpondyloArthritis (SpA) international Society (ASAS) Classification Criteria for Axial SpA (2009) (axSpA) [12], and the Classification Criteria for PsA (CASPAR) [13]. The data for this study comprised detailed demographic, clinical, and treatment information obtained from a complete review of medical records within one tertiary care rheumatology clinic during the period of January 2022 to December 2022.

Participants were required to be at least 18 years of age and possess a confirmed diagnosis of RA, AS, or PsA, as defined by established classification criteria [11]. Complete records of treatment regimens and diagnostic classifications (including biological disease modifying anti-rheumatic drugs (DMARDs), conventional DMARDs, non-steroidal anti-inflammatory drugs (NSAIDs), and corticosteroids), in addition to documented eye and skin color, were required for patient inclusion.

Skin color categorization utilized the Fitzpatrick system, assigning types 1-2 to fair skin, type 3 to light olive skin, type 4 to dark olive skin, type 5 to brown skin [14]. Two clinicians evaluated skin color by inspecting the inner surfaces of arms and legs which remained unexposed to the sun. Inter-rater reliability between the two clinicians was assessed using Cohen's kappa coefficient, with a value of 0.85 indicating strong agreement. Skin evaluation was performed by F.A. and E.K. in a double-blind manner. The patients' diagnoses and treatments were not known.

For ophthalmological examination, best corrected visual acuity was determined by Snellen's threshold, anterior segment examination by slit lamp biomicroscopy, fundus examination by ninety dioptre lens and intraocular pressure by Goldmann applanation tonometry. Both skin and eye color assessments were conducted in a double-blind manner; the evaluators (M.B. and G.S.) were blinded to patient diagnoses and treatments. The patients' diagnoses and treatments were not known. Eye colour was determined by determination of iris colour in slit lamp biomicroscopy. Eye colour classification was made according to the classification of Mackey et al. [15]. According to this classification, 3 main iris colour groups were determined as blue, hazel-green and brown. Mackey et al. subdivided these 3 main groups into 9 different colour groups. These were 1: light blue, 2: dark blue, 3: blue with peripupillary brown, 4: green, 5: green with peripheral brown ring, 6: centre brown, peripheral green, 7: light peripheral green, brown, 8: light brown, 9: dark brown. In addition, two groups were formed as light and dark iris colour. In the light group: 1, 3, 4, 5, 6, 7, 8; in the dark group: 2, 9. Patients with diseases affecting iris colour such as Waardenburg syndrome, Horner syndrome, Sturge Weber syndrome, Fuch heterochromic iridocyclitis, topical prostaglandin analogue users and those with a history of trauma to the iris were not included in the study.

The study excluded individuals exhibiting missing or incomplete data, comorbid autoimmune diseases (specifically systemic lupus erythematosus, Sjögren's syndrome, inflammatory bowel disease, or autoimmune thyroid disorders), or uncategorized pigmentation traits. The study protocol was approved by the relevant Gaziantep Islam Science and Technology University institutional ethics committee (Decision no: 370.35.02, Date: 26.02.2024), and all patient data were anonymized before analysis.

Statistical Analyses

Statistical analyses were conducted using R software (version 4.4.2), incorporating the packages rstatix, lavaan, flextable, and lavaanPlot for data processing and structural modeling. Shapiro-Wilk tests were used to assess the distribution of continuous variables. Group comparisons for normally distributed variables utilized independent samples t-tests and one-way ANOVAs. Conversely, non-normally distributed variables were analyzed via the Wilcoxon rank-sum or Kruskal-Wallis test, as applicable. Categorical variables were compared using the Pearson chi-square test or Fisher’s exact test. Statistical significance was defined as a two-tailed p-value less than 0.05.

To improve statistical power and reflect shared disease mechanisms, we analyzed RA, AS, and PsA as distinct conditions and also combined AS and PsA into a seronegative SpA group for secondary tests. Accordingly, comparisons and subgroup analyses

DOI: 10.5455/medscience.2025.07.193

were conducted both across three diagnostic groups (RA, AS, PsA) and across two groups (RA vs. SpA).

The associations between phenotypic traits and clinical outcomes were further examined through structural equation modeling (SEM). In the primary model, eye color (categorized as brown, blue, or green, and additionally classified as dark or light) and skin color (classified as white, light wheatish, dark wheatish, and dark-skinned) were included as independent variables. The diagnosis group (RA, AS, PsA) was modeled as a mediating variable, while the treatment group—comprising non-steroidal anti-inflammatory drugs (NSAIDs), disease modifying anti-rheumatic drugs (DMARDs), a single biologic agent, or multiple biologic agents—served as the dependent variable. To validate the robustness of the findings, a secondary SEM analysis was performed in which AS and PsA were merged into a single seronegative SpA category, referred to as the short diagnosis group.

Model fit was assessed using standard goodness-of-fit indices, including the Comparative Fit Index (CFI), Tucker–Lewis Index (TLI), Root Mean Square Error of Approximation (RMSEA), and Standardized Root Mean Residual (SRMR). Standardized regression coefficients (β) were estimated using a nonparametric bootstrapping method with 5,000 iterations. For each coefficient, standard errors, p-values, and 95% confidence intervals were reported. Results with $p<0.05$ were deemed statistically significant.

Results

Descriptive Analysis

The mean age of the overall study population (n=215) was calculated as 46.75±11.65 years. A statistically significant age difference ($p<0.001$) was observed between the RA group (mean age 51.41±11.68) and the SpA group (mean age 43.13±10.30). Of the total participants, 66.98% were women, showing a significantly higher representation in the RA group (79.79%) than the SpA group (57.02%). A detailed summary of demographic and clinical variables by diagnostic group is provided in Table 1.

Table 1. Distribution of demographic and pigmentation traits across RA, AS, and PsA

	Overall (n=215)	RA (n=94)	SpA			p - value
			AS (n=89)	PSA (n=32)	Total (n=121)	
Age	46.75±11.65	51.41±11.68	42.28±10.39	45.5±9.81	43.13±10.3	**<0.001**
Gender, n (%)						**<0.001**
Female	144 (66.98)	75 (79.79)	43 (48.31)	26 (81.25)	69 (57.02)	
Male	71 (33.02)	19 (20.21)	46 (51.69)	6 (18.75)	52 (42.98)	
Eye color, n (%)						**<0.001**
Brown	165 (76.74)	83 (88.30)	60 (67.42)	22 (68.75)	82 (67.77)	
Blue	30 (13.95)	4 (4.26)	19 (21.35)	7 (21.88)	26 (21.49)	
Green	20 (9.30)	7 (7.45)	10 (11.24)	3 (9.38)	13 (10.74)	
Eye color (Binary), n (%)						**<0.001**
Dark-colored eyes	164 (76.28)	83 (88.30)	59 (66.29)	22 (68.75)	81 (66.94)	
Light-colored eyes	51 (23.72)	11 (11.70)	30 (33.71)	10 (31.25)	40 (33.06)	
Skin color, n (%)						0.051
White	15 (6.98)	11 (11.70)	1 (1.12)	3 (9.38)	4 (3.31)	
Light wheatish	93 (43.26)	35 (37.23)	40 (44.94)	18 (56.25)	58 (47.93)	
Dark wheatish	95 (44.19)	41 (43.62)	45 (50.56)	9 (28.12)	54 (44.63)	
Dark-skinned	12 (5.58)	7 (7.45)	3 (3.37)	2 (6.25)	5 (4.13)	
Treatment group, n (%)						**<0.001**
DMARD	58 (26.98)	47 (50.00)	0 (0.00)	11 (34.38)	11 (9.09)	
≥1 biologic agent	92 (42.79)	34 (36.17)	51 (57.30)	7 (21.88)	58 (47.93)	
≥2 biologic agents	46 (21.40)	13 (13.83)	19 (21.35)	14 (43.75)	33 (27.27)	
NSAID	19 (8.84)	0 (0.00)	0 (0.00)	11 (34.38)	19 (15.70)	

Table presents the distribution of demographic variables, eye color (categorized as brown, blue, green; and binary classification as light- or dark-colored), skin color (white, light wheatish, dark wheatish, dark-skinned), and treatment groups across patients diagnosed with rheumatoid arthritis (RA), ankylosing spondylitis (AS), and psoriatic arthritis (PsA); The SpA group combines AS and PsA diagnoses for comparative purposes; Treatment groups include conventional DMARDs, biologic therapies (classified as ≥1 or ≥2 agents), and NSAIDs; Values are reported as means with standard deviations for continuous variables and as frequencies with percentages for categorical variables; The p-values indicate statistical significance for comparisons between the RA and SpA groups

DOI: 10.5455/medscience.2025.07.193

Brown eyes were the predominant eye color, with a prevalence of 76.74%. Analysis revealed a significant disparity ($p<0.001$) in the distribution of eye color across diagnostic groups. The prevalence of dark eyes was considerably higher in the RA cohort (88.30%) compared to the SpA cohort (66.94%). Consistently, SpA patients exhibited a greater prevalence of blue and green eyes. A majority of the observed skin tones fell within the light and dark wheatish ranges. While a trend toward significance was observed, no statistically significant difference in skin color was found between the RA and SpA cohorts ($p=0.051$).

Concerning treatment categorization, the SpA group demonstrated significantly higher use of biologic agents (75.21%) than the RA group (50.00%). DMARD usage predominated in the RA patient population (50%), in contrast to NSAID use, which was exclusive to the SpA group. Disease duration was significantly greater within the SpA group ($p<0.001$).

Separate analyses of RA, AS, and PsA subgroups showed significant differences in age ($p<0.001$) and sex distribution ($p<0.001$) across diagnostic categories. Significant associations ($p<0.05$ for all) were found between diagnosis and both eye color (categorical and binary) and skin color. The treatment group classifications showed a strong association with diagnosis ($p<0.001$).

Separate analysis of disease groups revealed mean ages of 42.28±10.39 years in the AS group and 45.5±9.81 years in the PsA group. A one-way ANOVA showed that the age distributions of the RA, AS, and PsA groups were significantly different ($F=16.31$, $df=2, 212$, $p<0.001$). Female patients constituted 48.31% of the AS group and 81.25% of the PsA group. Significant associations were found between sex and diagnostic categories through Pearson's Chi-square test ($\chi^2=23.94$). Notably, a significant association was observed between treatment modality and diagnostic category ($\chi^2=88.63$, $df=6$, $p<0.001$). Table 1 provides a comprehensive summary of these findings.

Structural Equation Model (SEM)

Analyzing RA, AS, and PsA separately in the initial SEM model (Table 2), a statistically significant negative association emerged ($\beta=-0.344$, $p<0.001$) between skin pigmentation and diagnostic assignment, implying a skewed representation where darker skin tones were disproportionately assigned to particular diagnostic groups. There was no significant association between eye color and diagnosis ($\beta=0.077$, $p=0.501$).

The analysis revealed that eye color significantly influenced the assignment to treatment groups ($\beta=0.300$, $p=0.041$), whereas skin color did not have any direct ($\beta=-0.114$, $p=0.381$) or indirect impact on the allocation. The results indicated that sex was the most influential factor in determining the treatment group ($\beta=0.947$, $p<0.001$), while diagnosis ($\beta=0.064$, $p=0.475$) and age ($\beta=-0.004$, $p=0.451$) were not statistically significant (Figure 1).

Table 2. Structural equation model demonstrating the effects of eye and skin color on diagnosis (RA, AS, PsA) and treatment group (NSAID, DMARD, biologic agents)

Variables	Estimate (β)	Standard error	Z-value	p-value	95% confidence interval
Eye color → diagnosis	0.077	0.115	0.672	0.501	(-0.145, 0.303)
Skin color → diagnosis	-0.344	0.065	-5.323	**<0.001**	(-0.473, -0.220)
Diagnosis → treatment group	0.064	0.090	0.714	0.475	(-0.121, 0.227)
Eye color → treatment group	0.300	0.147	2.044	**0.041**	(0.044, 0.629)
Skin color → treatment group	-0.114	0.130	-0.876	0.381	(-0.384, 0.122)
Age → treatment group	-0.004	0.006	-0.753	0.451	(-0.016, 0.006)
Sex → treatment group	0.947	0.245	3.861	**<0.001**	(0.514, 1.483)

Table displays the results of the structural equation model (SEM) evaluating the effects of eye color, skin color, age, and sex on diagnostic classification (RA, AS, PsA) and subsequent treatment group assignment (NSAID, DMARD, single or multiple biologic agents); Standardized regression coefficients (β), standard errors, Z-values, p-values, and 95% confidence intervals are reported for each path in the model; Statistically significant associations were found between skin color and diagnosis, and between eye color and treatment group; Sex demonstrated a strong and significant effect on treatment group allocation, whereas age and diagnosis showed no significant direct influence on treatment received

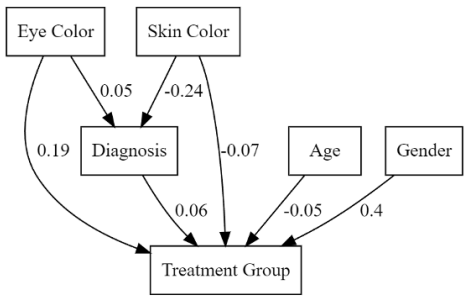

Figure 1. Structural Equation Model (SEM) diagram illustrating the effects of eye and skin color on diagnosis (RA, AS, PsA) and treatment group (NSAID, DMARD, biologic agents)

The secondary SEM model combined AS and PsA into a single SpA category (Table 3) and revealed a significant association between eye color ($\beta=0.282$, $p=0.037$) and skin color ($\beta=-0.298$, $p<0.001$) with the short diagnosis group. However, both features did not play a significant role in determining the distribution of treatment groups. The influence of sex on treatment decisions persisted strongly ($\beta=0.894$, $p=0.001$), with age showing no significant correlation ($\beta=-0.003$, $p=0.642$). While there were differences in eye and skin color among the treatment groups, these physical characteristics did not reliably determine treatment assignment in either SEM model (Figure 2).

DOI: 10.5455/medscience.2025.07.193

Table 3. Structural equation model demonstrating the effects of eye and skin color on diagnosis (RA, Spa) and treatment group (NSAID, DMARD, biologic agents)

Variables	Estimate (β)	Standard error	Z-value	p-value	95% confidence interval
Eye color → short diagnosis	0.282	0.136	2.082	**0.037**	(0.012, 0.555)
Skin color → short diagnosis	-0.298	0.072	-4.146	**<0.001**	(-0.445, -0.159)
Short diagnosis → treatment group	0.030	0.136	0.217	0.828	(-0.255, 0.282)
Eye color → treatment group	0.228	0.155	1.472	**0.141**	(-0.017, 0.587)
Skin color → treatment group	-0.116	0.136	-0.853	0.394	(-0.408, 0.128)
Age → treatment group	-0.003	0.006	-0.465	0.642	(-0.017, 0.008)
Sex → treatment group	0.894	0.260	3.438	**0.001**	(0.457, 1.475)

Table presents the results of a secondary structural equation model (SEM) in which ankylosing spondylitis (AS) and psoriatic arthritis (PsA) were combined into a single diagnostic category labeled as SpA; The model examines the effects of eye color, skin color, age, and sex on this simplified diagnostic classification (RA vs. SpA) and corresponding treatment group assignment (NSAID, DMARD, single or multiple biologic agents); Reported values include standardized regression coefficients (β), standard errors, Z-values, p-values, and 95% confidence intervals; Significant associations were found between both eye color and skin color with the short diagnosis group; However, neither variable showed a statistically significant effect on treatment group allocation; Sex remained a strong and significant predictor of treatment received, while age showed no significant effect

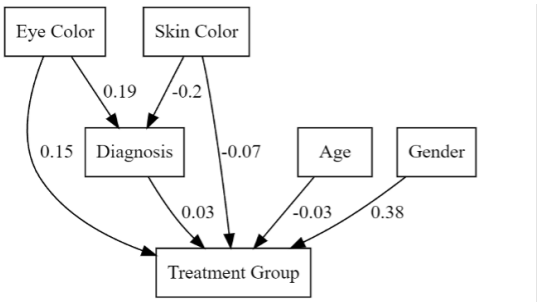

Figure 2. Structural Equation Model (SEM) diagram illustrating the effects of eye and skin color on diagnosis (RA, Spa) and treatment group (NSAID, DMARD, biologic agents)

Discussion

This study examined the association between phenotypic traits—specifically eye and skin color—and the diagnosis and management of inflammatory rheumatic diseases, including RA and SpA. The study found significant differences between RA and SpA groups in age, sex, eye and skin color, and treatment types. SEM analyses showed that sex was the strongest predictor of treatment group. Eye color was associated with diagnosis, while skin color was linked to diagnosis but not treatment.

Pigmentation Traits and Autoimmune Diseases

Existing literature indicates a differential prevalence of certain autoimmune diseases among individuals with varying skin tones [16]. Studies indicate a correlation between melanin-related genetic variations and immune system responses [17-19]. For instance, the identification of autoantigens relevant to vitiligo, an autoimmune disorder involving skin depigmentation, illustrates the complex relationship between pigmentation genetics and autoimmunity [20].

Studies of pigmentation traits demonstrate that both eye and skin color impact disease susceptibility and treatment outcomes [19,21]. Individuals with lighter iris pigmentation exhibit a heightened susceptibility to conditions such as age-related macular degeneration, underscoring the photoprotective function of melanin [22]. The link between immunity and pigmentation in vitiligo, an autoimmune disease causing melanocyte destruction, points to a combined genetic and environmental influence in its development [23].

A study by Pleasants et al. found a greater incidence of light-colored irises in individuals diagnosed with idiopathic pulmonary fibrosis (IPF), which has similar autoimmune processes as RA and AS [9]. This suggests that skin pigmentation could indirectly indicate systemic immune responses. Consistent with Hashemi et al.'s research, iris color correlated with ocular features like corneal thickness, possibly indicating broader anatomical/physiological differences impacting disease predisposition [10]. Furthermore, Jonnalagadda et al. pinpointed specific genes linked to skin and eye color that also affect the immune system, suggesting a common genetic basis for pigmentation and inflammatory illnesses [24]. In another study, reported that uveal melanoma provides more evidence for the idea that pigment genes might interact with the body's immune system [6].

Our findings highlight a notable disparity in SpA diagnostic categorization based on skin color, showing a higher prevalence of SpA diagnoses among individuals with darker skin. While skin color was more strongly associated with diagnosis, a statistically significant—though modest—relationship between eye color and diagnostic category also emerged.

Although pigmentation traits and autoimmune mechanisms have been theoretically linked, our findings do not reveal a consistent correlation between these traits and received treatments. Analysis of the model, which categorized RA, AS, and PsA as distinct diagnoses, revealed a statistically significant, albeit weak, association between eye color and treatment assignment. The aforementioned relationship was absent in the simplified comparison of RA and SpA, suggesting that the result may be an artifact of the model or subgroup heterogeneity. Conversely, neither model showed any direct or indirect link between skin color and the treatment received. Although these results do

DOI: 10.5455/medscience.2025.07.193

not support a direct role for pigmentation in current treatment strategies, they indicate the potential involvement of eye color, and possibly other phenotypic characteristics, in biological pathways influencing disease progression or therapeutic requirements. Further investigation is warranted, particularly with respect to larger and more heterogeneous samples. In addition to phenotypic traits, sex was found to play a dominant role in shaping received treatments.

Sex Differences in Autoimmune Disease Management

Studies consistently demonstrate a marked female preponderance in the occurrence of RA, PsA. Female patients represent approximately 70-75% of diagnosed RA cases, highlighting a considerable gender disparity in disease prevalence [25,26]. In contrast, male patients show a more aggressive disease course and higher rates of comorbidities, such as cardiovascular disease, than females, highlighting sex-based differences in disease pathophysiology [27,28]. Clinical manifestations and symptom severity in these disorders are further differentiated by sex [29,30]. Furthermore, mental health challenges more commonly reported among females, such as depression and anxiety, may complicate disease management and treatment adherence [7,28,31].

The pronounced influence of sex on treatment allocation observed in this study aligns with existing literature documenting sex-based disparities in autoimmune diseases. Notably, sex was consistently the most significant factor in determining treatment allocation. This finding aligns with extensive research highlighting how sex influences disease vulnerability, immune reactions, and treatment efficacy, with studies revealing distinct patterns between males and females [32-34]. The effects of autoimmune diseases differ between the sexes, with women facing a higher incidence, varied symptoms, and unique responses to therapy. These results highlight the importance of using sex-specific methods in both clinical practice and research. Moreover, sex hormones like estrogen and progesterone may affect immune function, thus altering disease risk and development [35]. Optimal treatment strategies and equitable healthcare outcomes necessitate the recognition and management of sex-based differences.

Given that sex was the most influential determinant of treatment group assignment, a deeper investigation into sex-based pharmacological dynamics is warranted. In our study, female patients showed significantly different treatment patterns, consistent with previous reports of sex-specific immune responses and drug metabolism. This suggests a potential need for sex-adapted therapeutic strategies in autoimmune diseases. Further analysis of pharmacodynamics and treatment adherence by sex may reveal additional mechanisms explaining this disparity.

Limitations

This study has several limitations that merit consideration. First, the relatively small sample size and the limited ethnic diversity of the cohort may reduce the generalizability of the findings to broader populations. Future multicenter studies with more heterogeneous populations are needed to validate and expand upon these observations. Second, the classification of eye and skin color was based on clinical assessment rather than objective measurement tools such as spectrophotometry or digital image analysis. Although standardized scales (Fitzpatrick for skin and Mackey et al. for eye color) were used and inter-rater reliability was strong (Cohen's kappa=0.85), the potential for observer bias remains. To enhance the reliability of pigmentation assessment, future research should incorporate objective methods such as spectrophotometry or digital image analysis to minimize observer bias. Third, several potential confounding variables—such as genetic background, socioeconomic status, and access to healthcare—were not included due to the retrospective nature of the study and limitations in the available data. These factors may influence both pigmentation traits and disease characteristics and should be accounted for in future research. Finally, the retrospective and single-center design inherently limits causal inference and external validity. Despite these limitations, the study offers novel insights and serves as an important foundation for future investigations exploring the intersection of phenotypic traits and autoimmune disease expression.

Conclusion

The findings of this study suggest that pigmentation traits, namely skin and eye color, are significantly associated with the diagnostic classification of inflammatory rheumatic diseases, showing a greater prevalence of SpA among those with darker skin tones. A modest association between eye color and diagnosis was also observed. However, the influence of either trait on received treatment proved inconsistent, suggesting that pigmentation is not presently a primary factor in therapeutic decision-making. In comparison, the most influential factor in treatment allocation was the patient's sex, consistent with recognized biological and clinical variations in disease manifestation and response between male and female individuals.

The collected data corroborates the hypothesis that observable phenotypic characteristics may indicate underlying genetic or immunological differences pertinent to the etiology of autoimmune diseases. Despite the unclear nature of the precise mechanisms involved, existing research suggests a relationship between pigmentation genes and immune system regulation, necessitating further study. Larger, multiethnic studies incorporating objective pigmentation assessments, genomic data, and environmental details are needed to clarify the biological importance of these associations and explore their use in personalized medicine.

Conflict of Interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical Approval
Gaziantep Islam Science and Technology University Faculty of Medicine Local Ethics Committee approved the study (Decision no: 370.35.02, Date: 26.02.2024).

DOI: 10.5455/medscience.2025.07.193

References

1. Pavan WJ, Sturm RA. The genetics of human skin and hair pigmentation. Annu Rev Genomics Hum Genet. 2019;20:41-72.
2. Sturm RA, Duffy DL. Human pigmentation genes under environmental selection. Genome Biol. 2012;13:248.
3. Solano F. Photoprotection and skin pigmentation: melanin-related molecules and some other new agents obtained from natural sources. Molecules. 2020;25:1537.
4. Sturm RA, Larsson M. Genetics of human iris colour and patterns. Pigment Cell Melanoma Res. 2009;22:544-62.
5. Subramanian A, Adderley NJ, Gkoutos GV, et al. Ethnicity-based differences in the incident risk of allergic diseases and autoimmune disorders: a UK-based retrospective cohort study of 4.4 million participants. Clin Exp Allergy. 2021;51:144-7.
6. Zhang H, Liu Y, Zhang K, et al. Validation of the relationship between iris color and uveal melanoma using artificial intelligence with multiple paths in a large Chinese population. Front Cell Dev Biol. 2021;9:713209.
7. Mease PJ, Bhutani MK, Hass S, et al. Comparison of clinical manifestations in rheumatoid arthritis vs. spondyloarthritis: a systematic literature review. Rheumatol Ther. 2022;9:331-78.
8. Sharma SD, Leung SH, Viatte S. Genetics of rheumatoid arthritis. Best Pract Res Clin Rheumatol. 2024;38:101968.
9. Pleasants RA, Bedoya A, Boggan JC, et al. The eyes have it—for idiopathic pulmonary fibrosis: a preliminary observation. Pulm Ther. 2022;8:327-31.
10. Hashemi H, Pakzad R, Yekta A, et al. . Distribution of iris color and its association with ocular diseases in a rural population of Iran. J Curr Ophthalmol. 2019;31:312-8.
11. Aletaha D, Neogi T, Silman AJ, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum. 2010;62:2569-81.
12. Rudwaleit M, van der Heijde D, Landewé R, et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. Ann Rheum Dis. 2009;68:777-83. Erratum in: Ann Rheum Dis. 2019;78:e59.
13. Taylor W, Gladman D, Helliwell P, et al. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheum. 2006;54:2665-73.
14. Fitzpatrick T. Sun and skin. Journal de Medecine Esthetique. 1975;2:33-4.
15. Mackey DA, Wilkinson CH, Kearns LS, Hewitt AW. Classification of iris colour: review and refinement of a classification schema. Clin Exp Ophthalmol. 2011;39:462-71.
16. McKenzie S, Brown-Korsah JB, Syder NC, et al. Variations in genetics, biology, and phenotype of cutaneous disorders in skin of color. Part II: differences in clinical presentation and disparities in cutaneous disorders in skin of color. J Am Acad Dermatol. 2022;87:1261-70.
17. Kim SY, Fargallo JA, Vergara P, Martínez-Padilla J. Multivariate heredity of melanin-based coloration, body mass and immunity. Heredity (Edinb). 2013;111:139-46.
18. Koike S, Yamasaki K. Melanogenesis connection with innate immunity and toll-like receptors. Int J Mol Sci 2020;21:9769.
19. Speeckaert R, Belpaire A, Speeckaert M, van Geel N. The delicate relation between melanocytes and skin immunity: a game of hide and seek. Pigment Cell Melanoma Res. 2022;35:392-407.
20. Waterman EA, Gawkrodger DJ, Watson PF, et al. Autoantigens in vitiligo identified by the serological selection of a phage-displayed melanocyte cDNA expression library. J Invest Dermatol. 2010;130:230-40.
21. Del Bino S, Duval C, Bernerd F. Clinical and biological characterization of skin pigmentation diversity and its consequences on UV impact. Int J Mol Sci. 2018;19:2668.
22. Godínez-Chaparro JA, Roldán-Marín R, Soto-Mota A, Calzada-Mendoza CC. Dermatoscopic patterns in childhood vitiligo and their association with reflectance confocal microscopy findings. Dermatol Pract Concept. 2023;13:e2023306.
23. Seviiri M, Law MH, Ong JS, et al. A multi-phenotype analysis reveals 19 susceptibility loci for basal cell carcinoma and 15 for squamous cell carcinoma. Nat Commun. 2022;13:7650.
24. Jonnalagadda M, Faizan MA, Ozarkar S, et al. A genome-wide association study of skin and iris pigmentation among individuals of South Asian Ancestry. Genome Biol Evol. 2019;11:1066-76.
25. Maranini B, Bortoluzzi A, Silvagni E, Govoni M. Focus on sex and gender: what we need to know in the management of rheumatoid arthritis. J Pers Med. 2022;12:499.
26. Xu Y, Wu Q. Prevalence trend and disparities in rheumatoid arthritis among US adults, 2005-2018. J Clin Med. 2021;10:3289.
27. Abisheva S, Amangeldiyeva Z, Serikova Z. Analysis of risk factors for the development of cardiovascular diseases in patients with rheumatoid arthritis, depending on gender. J Clin Med Kaz. 2020;2:34-40.
28. Nourisson C, Soubrier M, Mulliez A, et al. Impact of gender on the response and tolerance to abatacept in patients with rheumatoid arthritis: results from the 'ORA'registry. RMD Open. 2017;3:e000515.
29. Kareem O, Ahmad HS, Ijaz B, Altaf S. Frequency of depression in patients with rheumatoid arthritis. Professional Med J. 2020;27:646-50.
30. Kozłowska KA, Formanowicz D, Bączyk G. The link between the demographic and clinical factors and fatigue symptoms among rheumatoid arthritis patients. Int J Environ Res Public Health. 2022;19:14681.
31. Lada G, Chinoy H, Talbot PS, et al. Associations between psoriatic arthritis and mental health among patients with psoriasis: a replication and extension study using the British Association of Dermatologists Biologics and Immunomodulators Register (BADBIR). Skin Health Dis. 2022;2:e149.
32. Eder L, Mylvaganam S, Pardo Pardo J, et al. Sex-related differences in patient characteristics, and efficacy and safety of advanced therapies in randomised clinical trials in psoriatic arthritis: a systematic literature review and meta-analysis. Lancet Rheumatol. 2023;5:e716-27.
33. Koehm M, Foldenauer AC, Rossmanith T, et al. Differences in treatment response between female and male psoriatic arthritis patients during IL-12/23 therapy with or without methotrexate: post hoc analysis of results from the randomised MUST trial. RMD Open. 2023;9:e003538.
34. Lubrano E, Scriffignano S, Fatica M, et al. Psoriatic arthritis in males and females: differences and similarities. Rheumatol Ther. 2023;10:589-99.
35. Merrheim J, Villegas J, Van Wassenhove J, et al. Estrogen, estrogen-like molecules and autoimmune diseases. Autoimmun Rev. 2020;19:102468.