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ORIGINAL PAPER

DECIPHERING HLA-LINKED IMMUNE DYSREGULATION IN PSORIATIC ARTHRITIS: A MOLDOVAN COHORT STUDY

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Abstract

Introduction. Psoriatic arthritis (PsA) is a chronic inflammatory disease influenced by genetic and immune factors. Human leukocyte antigen (HLA) class I molecules have been linked to PsA susceptibility and severity, yet their role in Eastern European populations remains unclear.
The objective of the study was to assess HLA allele associations with immune cell subsets, immunoglobulin levels, and circulating immune complexes (CICs) in Moldovan PsA patients.
Material and methods. A cross-sectional study of 103 PsA patients was conducted, stratified into two groups: with psoriasis (n=76) and without psoriasis (n=27). HLA typing, T (CD4+, CD8+) and B (CD22+) cell phenotyping, and immunoglobulin (IgA, IgG, IgM) and CIC measurements were performed. Statistical analyses included chi-square, t-tests, ANOVA, and correlation assessments.
Results. HLA-B27, HLA-B62, and HLA-B8 were associated with aggressive PsA phenotypes, elevated IgG levels, and systemic immune activation. Protective alleles HLA-A2 and HLA-A3 correlated with lower disease activity, reduced CICs, and immunomodulatory effects on T and B lymphocytes. The interaction between HLA-A2/A8 and CD8+ T cells highlighted

Résumé

Déchiffrer la dysrégulation immunitaire liée au HLA dans l'arthrite psoriasique: une étude de cohorte moldave

Introduction. L'arthrite psoriasique (APs) est une maladie inflammatoire chronique influencée par des facteurs génétiques et immunitaires. Les molécules de l'antigène des leucocytes humains (HLA) de classe I sont associées à la susceptibilité et à la sévérité de la APs, mais leur rôle dans les populations d'Europe de l'Est reste incertain.
L'objectif de l'étude était à évaluer les associations des allèles HLA avec les sous-populations de cellules immunitaires, les niveaux d'immunoglobulines et les complexes immuns circulants (CIC) chez les patients moldaves atteints de APs.
Matériel et méthodes. Une étude transversale a été menée auprès de 103 patients atteints de APs, répartis en deux groupes: avec psoriasis (n=76) et sans psoriasis (n=27). Le typage HLA, la phénotypage des cellules T (CD4+, CD8+) et B (CD22+), ainsi que les dosages des immunoglobulines (IgA, IgG, IgM) et des CIC ont été réalisés. Les analyses statistiques comprenaient les tests du chi-carré, les tests t, l'ANOVA et les évaluations de corrélation.

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distinct immune regulatory mechanisms in PsA with and without psoriasis.
Conclusions. HLA alleles significantly influence PsA severity and immune dysregulation in the Moldovan population. HLA-B27-related variants drive inflammatory responses, while HLA-A2 and HLA-A3 exert protective effects. These findings provide insights into region-specific immunogenetic mechanisms and potential personalized therapeutic targets.

Keywords: psoriatic arthritis, HLA, immune response, CD4+, CD8+, immunoglobulins.

List of abbreviations:
ANOVA – analysis of variance
CASPAR – classification criteria for psoriatic arthritis
CD – cluster of differentiation
CIC – circulating immune complex
DAPSA – disease activity in psoriatic arthritis
ELISA – enzyme-linked immunosorbent assay
HLA – human leukocyte antigen
Ig – immunoglobulin
IgA – immunoglobulin A
IgG – immunoglobulin G
IgM – immunoglobulin M
MHC – major histocompatibility complex
PsA – psoriatic arthritis
PSO – psoriasis
SD – standard deviation

Résultats. Les allèles HLA-B27, HLA-B62 et HLA-B8 étaient associés à des formes agressives de APs, à des niveaux élevés d'IgG et à une activation immunitaire systémique. Les allèles protecteurs HLA-A2 et HLA-A3 étaient corrélés à une activité réduite de la maladie, à une diminution des CIC et à des effets immunomodulateurs sur les lymphocytes T et B. L'interaction entre HLA-A2/A8 et les cellules T CD8+ a révélé des mécanismes distincts de régulation immunitaire selon la présence ou l'absence du psoriasis.
Conclusions. Les allèles HLA influencent significativement la sévérité de la APs et la dysrégulation immunitaire dans la population moldave. Les variants associés à HLA-B27 favorisent les réponses inflammatoires, tandis que HLA-A2 et HLA-A3 exercent des effets protecteurs. Ces résultats apportent des perspectives sur les mécanismes immunogénétiques spécifiques à cette population et sur d'éventuelles cibles thérapeutiques personnalisées.

Mots-clés: arthrite psoriasique, HLA, réponse immunitaire, CD4+, CD8+, immunoglobulines

Introduction

Psoriatic arthritis (PsA) is a chronic inflammatory arthropathy associated with psoriasis, characterized by synovial and entheseal inflammation, leading to progressive joint damage[1,2]. The interplay between genetic susceptibility and immune dysregulation plays a central role in its pathogenesis[3,4]. The major histocompatibility complex (MHC), particularly human leukocyte antigen (HLA) class I molecules, has been implicated in disease susceptibility, severity, and clinical heterogeneity[5]. Despite extensive studies in Western[6,7] and Central European[8,9] populations, the immunogenetic profile of PsA in Eastern European cohorts, particularly in the Republic of Moldova, remains unexplored.

HLA associations in PsA vary significantly across populations, with HLA-B27, HLA-B38, and HLA-B39 being linked to axial and peripheral joint involvement[10-12], while HLA-Cw6 is predominantly associated with cutaneous psoriasis (PSO)[13,14]. However, the influence of other HLA alleles, such as HLA-A2 and HLA-A3, on immune modulation and disease progression remains poorly defined. Studies have shown that HLA-B27 confers a higher risk for spondyloarthropathies, yet its unique role in PsA, especially in conjunction with alleles like HLA-B62 or HLA-B8, warrants further investigation[11,12]. Additionally, the potential protective effects of certain HLA alleles and their interaction with T and B lymphocyte subsets in PsA pathogenesis are not well understood[15].

Previous studies indicate substantial heterogeneity in HLA allele distributions among different ethnic groups, emphasizing the need for region-specific research[6-9]. While Western European studies have reported associations with HLA-A2 and HLA-B27[6,7], Southern European populations have highlighted links to HLA-A3, HLA-B17, and HLA-B27[9]. This variability underscores the necessity of investigating PsA-related HLA associations within the Moldovan population to better understand its genetic predisposition and immune response mechanisms.

Despite advances in the immunogenetic characterization of PsA, the precise mechanisms by which HLA alleles influence immune cell interactions remain insufficiently elucidated. CD4+ and CD8+ T lymphocytes, along with B cell activation, play key roles in PsA pathogenesis[15,16]. Identifying specific

Table 1. General Characteristics of the Study Population

Characteristics	Overall Cohort (n=103)	Group I (n=76)	Group II (n=27)
Male/Female, n	57/46	41/35	16/11
Mean age, years ± SD	46.4 ± 3.1	45.16 ± 2.1	47.6 ± 2.3
Mean PsA duration, years ± SD	6.1 ± 1.4	5.8 ± 1.7	6.3 ± 2.4
Mean duration of PSO, years ± SD	-	15.5 ± 1.4	-

Note: Data are presented as mean values ± standard deviation (SD) unless otherwise specified. Group I include patients with PsA and concomitant PSO, while Group II consists of patients with PsA but no PSO. Differences between groups were not statistically significant ($p>0.05$) for demographic variables and disease duration.

HLA alleles that regulate immune cell subsets can offer insights into disease progression and potential therapeutic targets. Furthermore, the association between HLA profiles and immunoglobulin synthesis or circulating immune complex (CIC) formation in PsA remains largely unexplored.

The objective of the study was to analyze the associations between HLA alleles and immune cell subsets, immunoglobulin levels and circulating immune complexes in patients with PsA. By evaluating these interactions, this research aims to identify HLA markers that may influence disease susceptibility, severity, and immunological response patterns, providing insights into potential immunomodulatory mechanisms and personalized therapeutic strategies for PsA in the Moldovan population.

Materials and methods

Study Design and Patient Selection

This cross-sectional study included a total of 103 patients diagnosed with PsA according to the Classification Criteria for Psoriatic Arthritis (CASPAR, 2006)[17]. The study cohort was stratified into two distinct groups: Group I – 76 patients with PsA and concomitant PSO; Group II – 27 patients with PsA without PSO.

The patients were recruited from the Rheumatology and Arthrology Departments of "Timofei Mosneaga" Republican Clinical Hospital and "The Holy Trinity" Municipal Clinical Hospital in Chisinau, Republic of Moldova, over a 9-year period (2015-2024). Inclusion criteria: confirmed diagnosis of PsA based on CASPAR criteria (2006); for Group I – presence of PSO in a stable phase; for group II – PsA without any clinical evidence of PSO. Exclusion criteria: failure to meet CASPAR diagnostic criteria; presence of other autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus); severe decompensated chronic conditions (e.g., diabetes mellitus, viral hepatitis, cirrhosis, hematologic malignancies, nephrological disorders, advanced cardiovascular diseases).

Clinical and Demographic Characteristics

Baseline demographic and clinical characteristics of the enrolled patients are presented in Table 1. Both groups were comparable in terms of age, sex distribution, and disease duration ($p>0.05$).

Laboratory and Immunological Assessments

Immunological profiles and HLA associations were evaluated through flow cytometry for T and B lymphocyte subsets (CD3+, CD4+, CD8+, CD22+), ELISA for serum immunoglobulins (IgA, IgM, IgG), turbidimetry for circulating immune complexes (CICs), and microlymphocytotoxicity assays for HLA class I and II antigen typing.

Statistical Analysis

Data were analyzed using STATISTICA 7.0. Chi-square (χ^2) tests were applied for categorical comparisons, while t-tests and ANOVA assessed continuous variables. Pearson and Spearman correlations evaluated immunological-genetic relationships, and factorial ANOVA examined interactions between independent variables and clinical outcomes. Statistical significance was set at $p<0.05$, with p-values further categorized as highly significant ($p<0.0001$) and moderately significant ($p<0.005$-0.05) to refine the interpretation of results.

Results

Correlation of T lymphocyte subsets with HLA antigen variants

Correlation analysis indicated no statistically significant relationship between total CD3+ T lymphocyte counts and HLA antigen variants ($p>0.05$). However, distinct variations were observed in CD4+ T lymphocyte distribution. In Group I, significant associations between CD4+ T cell levels and specific HLA alleles were identified ($p=0.00513$). In contrast, no such correlation was present in Group II ($p>0.05$). HLA-B27, HLA-B27/B8, and HLA-B27/A3 were associated with increased CD4+ T cell activity ($p<0.01$), whereas HLA-A2 and HLA-A3 correlated with low or normal CD4+ T cell levels, indicating their potential protective role in immune response modulation (Figure 1).

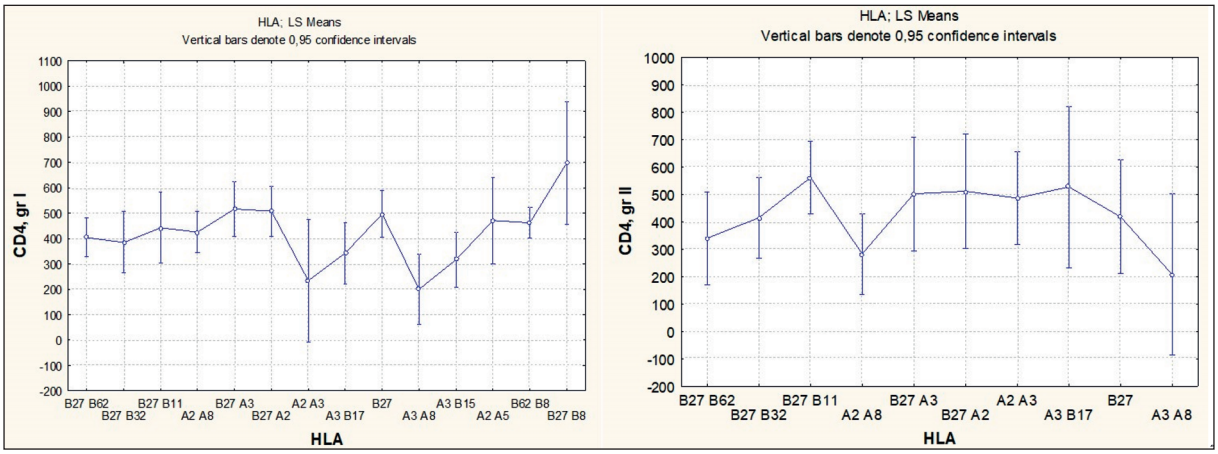


Figure 1. Graphical representation of factorial correlations between HLA antigens and mean absolute CD4+ T lymphocyte values in patients with PsA with and without PSO.

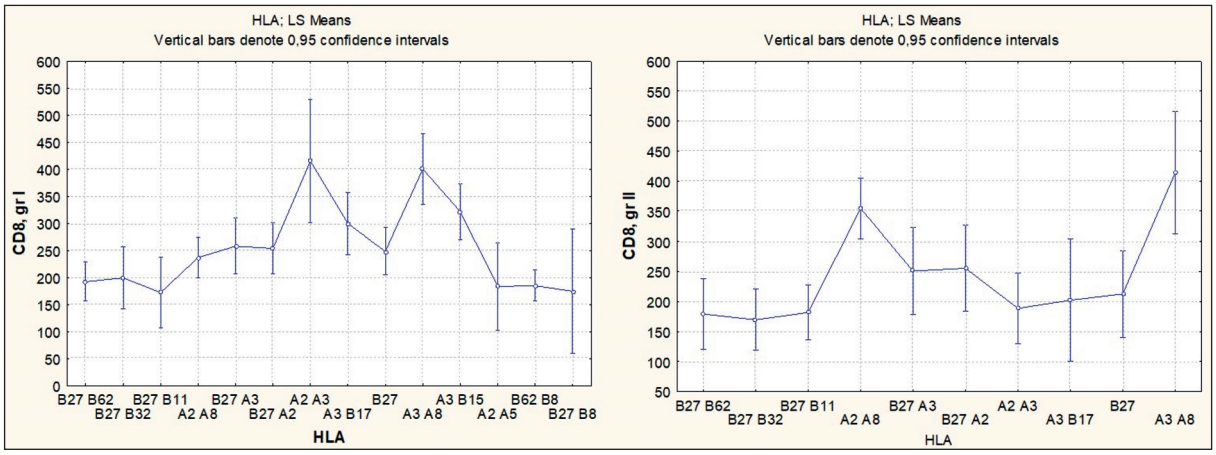


Figure 2. Factorial correlation between HLA antigens and mean absolute CD8+ T lymphocyte values in patients with PsA with and without PSO.

The analysis of CD8+ T lymphocytes demonstrated a significant factorial correlation with various HLA antigen sets, revealing a notable decline in circulating CD8+ T cells. This reduction is likely attributed to the migration of CD8+ T cells into inflammatory sites or the onset of secondary immunodeficiency, particularly in association with HLA-A2/A3 and HLA-A2/A8 (Figure 2). These findings suggest that CD8+ T cells play a crucial role in sustaining localized inflammation in PsA.

A factorial ANOVA confirmed significant differences in HLA antigen distributions affecting CD8+ T cell counts ($p<0.0001$). HLA-B27/B62, HLA-B27/B32, HLA-B27/B11, and HLA-B62/B8 were strongly associated with aggressive PsA phenotypes, correlating with increased DAPSA scores and inflammation. Conversely, HLA-A2/A3 and HLA-A2/A8 had protective effects by reducing DAPSA scores and CD3+/CD4+ T lymphocyte counts but exhibited distinct effects on CD8+ T cells.

In PsA with PSO, HLA-A2/A8 was linked to lower CD8+ T cell levels, suggesting an immunosuppressive effect that mitigates joint inflammation, whereas in PsA without PSO, this allele correlated with increased CD8+ T cells. HLA-A2/A3 showed an opposite trend, lowering CD8+ T cells while maintaining inflammation control. These patterns suggest a complex interplay between CD4+ and CD8+ T cells, where HLA-A2/A8 promotes CD4+ T cell proliferation, potentially inhibiting CD8+ T cell maturation in PsA with PSO. In PsA without PSO, HLA-A2/A3 was linked to increased CD8+ T cell proliferation, possibly suppressing CD4+ T cells.

These findings underscore the crucial role of CD8+ T cells in PsA severity and immune modulation, highlighting HLA-A2/A3 and HLA-A2/A8 as key regulators of immune balance and potential therapeutic targets.

Correlation between HLA antigens and CD22+ B lymphocytes

The analysis of the relationship between HLA antigens and CD22+ B lymphocytes highlighted the significant influence of HLA-B27/B11, HLA-B27/B32,

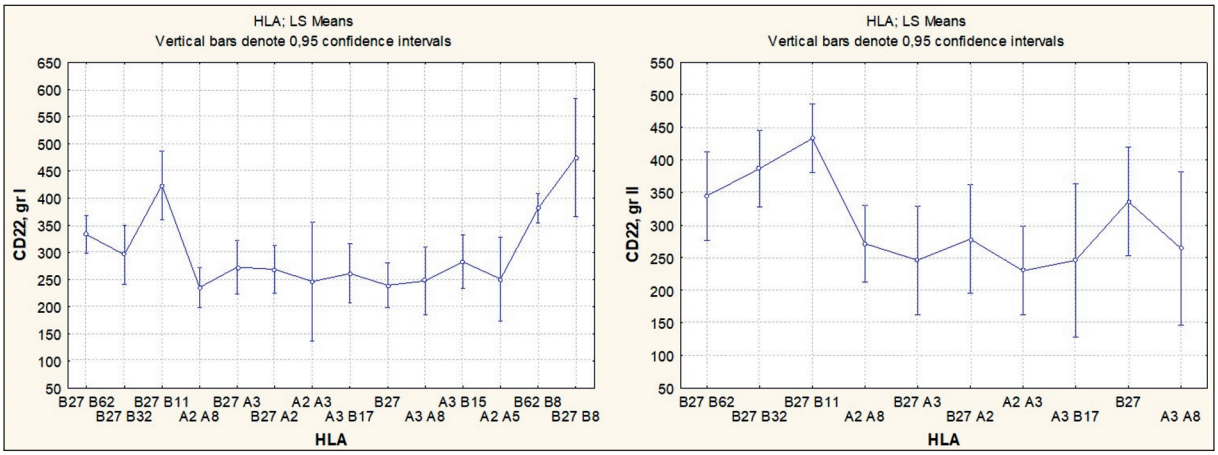


Figure 3. Factorial correlation between HLA antigens and mean absolute CD22+ B lymphocyte values in patients with PsA with and without PSO.

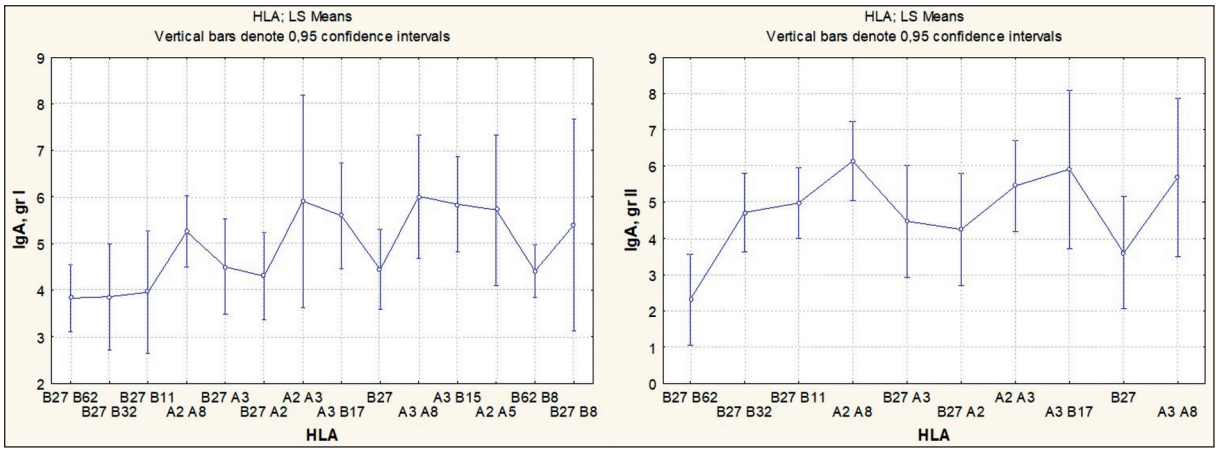


Figure 4. Factorial correlations between HLA antigens and mean serum IgA concentrations in patients with PsA with and without PSO.

HLA-B27/B8, and HLA-B62/B8 in determining severe forms of PsA. Factorial analysis using ANOVA with constrained σ-parameterization demonstrated a strong association between these HLA variants and increased CD22+ B lymphocyte proliferation in both PsA subgroups: Group I ($p<0.0001$) and Group II ($p<0.005$).

The proliferation of B cells was strongly associated with increased disease activity, evidenced by accelerated immunoglobulin synthesis and elevated serum immunoglobulin levels. This effect was most pronounced in severe clinical presentations, including mutilating and polyarticular PsA, indicating an amplified humoral immune response. These findings emphasize the relevance of targeting B cell-mediated pathways and specific HLA antigen interactions for optimizing therapeutic strategies in severe PsA cases (Figure 3).

Influence of HLA antigens on serum immunoglobulin levels

The study further demonstrated that specific HLA antigens play a critical role in modulating serum immunoglobulin concentrations, particularly IgA, in PsA patients. Factorial analysis confirmed a significant correlation ($p<0.05$) between certain HLA antigen sets and elevated IgA levels, contributing to enhanced inflammatory activity.

HLA-B8, recognized for its role in B-cell hyperactivation, was frequently associated with markedly increased IgA concentrations. This effect was further amplified in the presence of HLA-B27 and HLA-B62, suggesting a synergistic mechanism that intensifies autoimmune responses, particularly in severe PsA subtypes, such as polyarticular and mutilant forms.

Protective HLA antigens, such as HLA-A2 and HLA-A3, were associated with lower serum immunoglobulin levels, suggesting a potential role in mitigating systemic inflammation and modulating disease severity. Figure 4 illustrates the factorial correlations between HLA antigens and mean serum IgA concentrations, reinforcing the observed findings and providing insights into immunological mechanisms underlying PsA. These associations highlight possible pathways for personalized therapeutic interventions.

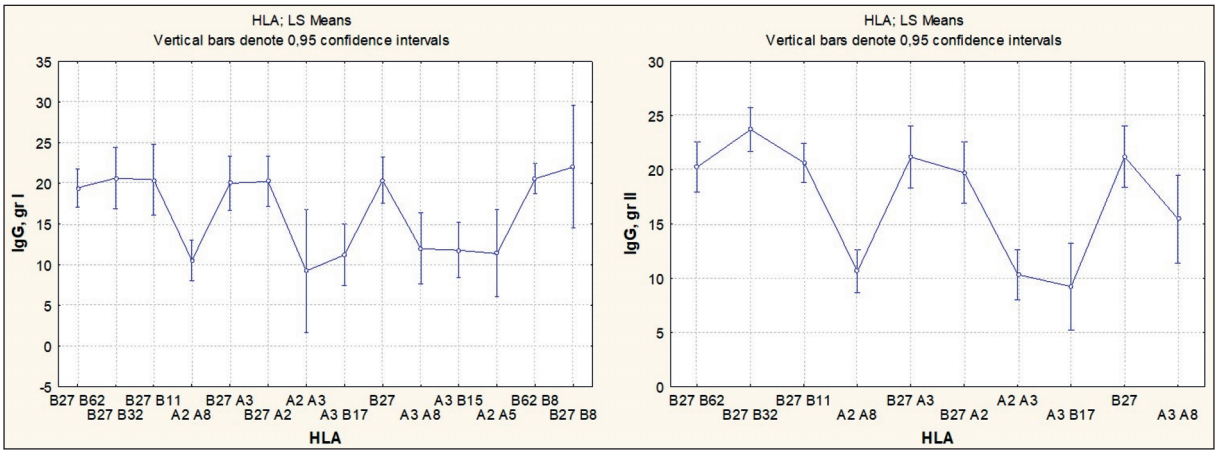


Figure 5. Factorial correlation between HLA antigens and mean absolute IgG concentrations in patients with PsA with and without PSO.

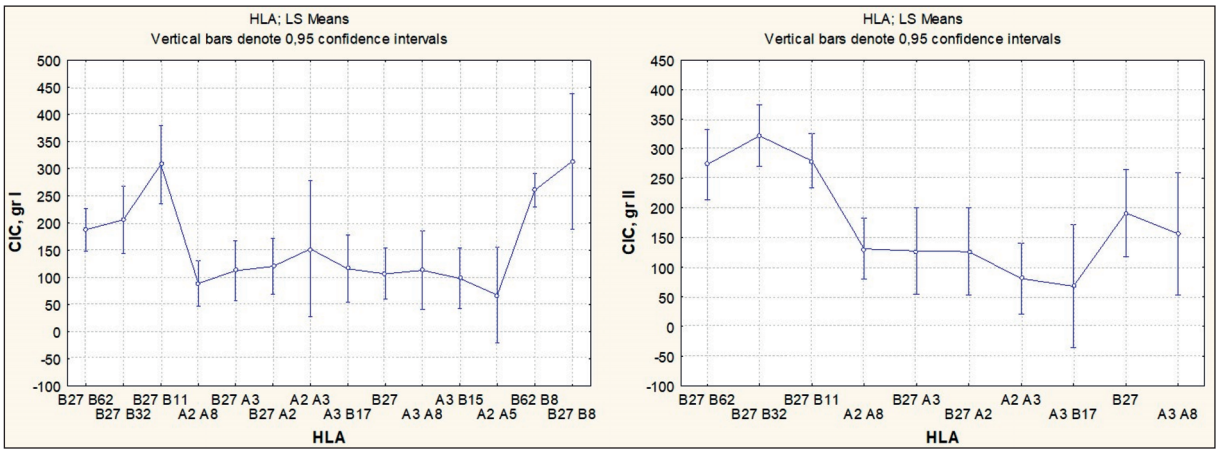


Figure 6. Factorial correlation between HLA antigens and mean absolute CIC concentrations in patients with PsA with and without PSO.

HLA antigen sets, including HLA-A2/A3 and HLA-A2/A8, were correlated with higher IgA concentrations, indicative of a moderated immune response and a potential link to milder PsA manifestations. Conversely, HLA-B27, HLA-B27/B62, HLA-B27/B32, and HLA-B62/B8 were primarily associated with normal or reduced IgA levels, supporting their role in more aggressive disease phenotypes, potentially driven by alternative inflammatory pathways. Unexpectedly, in Group II, HLA-B27/B32 and HLA-B27/B11 were linked to elevated IgA levels, suggesting a shift in immune activity towards humoral responses due to CD8+ T cell suppression.

The observed relationships between HLA antigens and serum IgA levels underscore the intricate balance of immune responses in PsA. Protective HLA alleles appear to contribute to a more regulated humoral immune response, whereas those associated with aggressive PsA may drive alternative inflammatory pathways. Further investigations are needed to elucidate the underlying mechanisms and their impact on disease progression and severity.

The analysis of serum IgM levels revealed no significant associations with HLA antigen profiles ($p>0.05$), indicating that IgM concentrations are not directly influenced by the immunogenetic background and may play a less pivotal role in PsA pathogenesis.

In contrast, factorial correlation analysis identified a strong association between serum IgG concentrations and specific HLA antigens ($p<0.0001$) (Figure 5). HLA variants linked to aggressive PsA subtypes, including HLA-B27/B62, HLA-B27/B32, HLA-B27/B11, HLA-B27, and HLA-B62/B8, were associated with elevated IgG levels, indicating systemic immune hyperactivation and more severe clinical progression. Conversely, protective antigens such as HLA-A2/A3 and HLA-A2/A8 correlated with normal or lower IgG levels, suggesting a reduced inflammatory burden and milder disease course.

Impact of HLA antigens on CIC

Further factorial correlation analysis distinguished protective HLA alleles from those associated

with heightened systemic inflammation, based on CIC concentrations (Figure 6).

Protective HLA variants (HLA-A2/A8, HLA-B27/A3, HLA-B27/A2, HLA-A2/A3, HLA-A3/B17) were linked to lower CIC levels ($p<0.0001$), indicating reduced systemic immune activity. In contrast, high-risk alleles (HLA-B27/B62, HLA-B27/B32, HLA-B27/B11, HLA-B62/B8) correlated with elevated CIC concentrations, suggesting a role in systemic inflammation.

Our research in the Moldovan population identified arthritogenic HLA alleles in PsA, including HLA-B27, HLA-B11, HLA-B8, HLA-A2, HLA-A3, HLA-A5, HLA-A8, HLA-B32, and HLA-B62. While their overall distribution did not differ significantly between patients with and without PSO, their prevalence varied by PsA subtype and skin involvement.

HLA antigens also influenced immunocellular status. No significant correlation was found with total T lymphocytes (CD3+), but clear patterns emerged in CD4+ and CD8+ subsets. In Group I, protective alleles were associated with CD4+ T cell proliferation and decreased CD8+ counts, while in Group II, aggressive HLA alleles correlated with CD8+ expansion and secondary CD4+ reduction.

These findings highlight distinct immune activation pathways shaped by specific HLA alleles, reinforcing their impact on disease severity and immune response in PsA.

Discussion

Our findings reinforce the pivotal role of HLA antigens in modulating the immunopathogenesis of PsA. The observed associations between specific HLA alleles and immune cell subsets, immunoglobulin levels, and CICs provide critical insights into disease heterogeneity and severity. These findings align with previous reports[15] on the genetic predisposition of PsA but also introduce novel insights into region-specific immunogenetic patterns, particularly in the Moldovan population.

HLA Associations and Disease Severity

The strong correlation between HLA-B27 and severe PsA phenotypes corroborates prior research highlighting its role in axial and peripheral joint involvement. Our study extends these observations by demonstrating that HLA-B27 in combination with other alleles, such as HLA-B27/B62, HLA-B27/B32, and HLA-B27/B8, is associated with aggressive disease manifestations, including high DAPSA scores, systemic inflammation, and alterations in T and B cell subsets. These results are consistent with studies in Scandinavian[11] and Southern European[8,9] populations, where HLA-B27 has been linked to more severe disease courses and higher prevalence of extra-articular involvement[18,19].

Interestingly, our data suggest that HLA-B27-positive patients exhibit a significant reduction in CD8+ T cell counts, a finding that aligns with the hypothesis that HLA-B27 misfolding and endoplasmic reticulum stress contribute to immune dysregulation[15]. The presence of secondary immunodeficiency features in these patients further supports the concept that HLA-B27 may alter T cell homeostasis, exacerbating systemic inflammatory responses[11,20].

Protective Effects of HLA-A2 and HLA-A3

Our study highlights the immunomodulatory role of HLA-A2 and HLA-A3, which were associated with lower DAPSA scores and a more controlled immune response. The protective effect of these alleles was evident in their association with reduced serum immunoglobulin levels and lower CIC concentrations. These findings are in line with previous reports suggesting that certain HLA class I alleles exert protective effects by modulating antigen presentation and T cell activation[21,22].

A notable observation was the differential impact of HLA-A2/A3 and HLA-A2/A8 on CD8+ T cells. In PsA patients with PSO, HLA-A2/A8 was linked to a reduction in CD8+ T cell levels, suggesting an immunosuppressive effect that mitigates joint inflammation. Conversely, in patients without PSO, this antigen set correlated with increased CD8+ T cell counts. Meanwhile, HLA-A2/A3 demonstrated an opposite trend, lowering CD8+ T cell levels while maintaining inflammation control. These findings highlight the complex interplay between HLA alleles and T cell subsets, warranting further investigation into their functional implications in PsA pathogenesis.

B Cell Activation and Humoral Immune Responses

The role of B cells in PsA pathogenesis has gained increasing attention, and our results provide further evidence supporting their contribution to disease activity. HLA-B27/B11, HLA-B27/B32, and HLA-B27/B8 were significantly associated with CD22+ B lymphocyte proliferation and elevated immunoglobulin synthesis, particularly IgA. These associations align with studies demonstrating that B cell activation and autoantibody production contribute to PsA progression[9,12,18].

Moreover, the correlation between high-risk HLA alleles and increased CIC levels suggests that immune complex-mediated inflammation may be a key driver of systemic immune activation in PsA. The involvement of HLA-B27 in this process further supports its role in promoting chronic inflammation

through persistent antigen presentation and aberrant immune responses[5,8,20,23]. In contrast, protective HLA-A2 and HLA-A3 alleles were associated with lower CIC concentrations, reinforcing their potential role in attenuating systemic immune activation.

Comparison with Other Populations

HLA associations in PsA vary significantly across ethnic groups, underscoring the importance of region-specific studies. Our findings share similarities with reports from Northern European populations, where HLA-B27, HLA-B62, and HLA-B8 are frequently implicated in severe PsA phenotypes[4,5,11,20]. However, the prominence of HLA-A2 and HLA-A3 in our cohort suggests unique immunogenetic characteristics within the Moldovan population.

Unlike studies in Mediterranean populations, where HLA-B38 and HLA-B39 are strongly associated with PsA[12,15,20], these alleles were not prevalent in our cohort. This discrepancy highlights the influence of genetic background and environmental factors in shaping PsA susceptibility and clinical presentation. Furthermore, the differential distribution of HLA alleles in patients with and without PSO suggests distinct immunopathogenic mechanisms underlying PsA subtypes.

Limitations of the study. Despite the significant insights provided, this study has certain limitations. The relatively small sample size, particularly in Group II (PsA without PSO), may limit the generalizability of the findings. Larger cohort studies are necessary to validate these observations and refine the understanding of HLA-related immunogenetic mechanisms in PsA. Additionally, while the study establishes associations between HLA alleles and immune parameters, functional studies are needed to elucidate the precise molecular mechanisms by which these alleles modulate immune responses. Another limitation is the retrospective nature of data collection, which may introduce selection bias.

Conclusions

This study highlights the impact of HLA associations on immune responses and disease severity in PsA. HLA-B27 and its variants (HLA-B27/B62, HLA-B27/B32, HLA-B27/B8) were linked to aggressive phenotypes, systemic inflammation, and immune dysfunction, particularly through CD8+ T cell reduction and B cell activation. In contrast, HLA-A2 and HLA-A3 exhibited protective effects, correlating with lower DAPSA scores, reduced immunoglobulin levels, and fewer circulating immune complexes. The differential impact of HLA-A2/A3 and HLA-A2/A8 on CD8+ T cells underscore the complexity of immune regulation. Unique HLA distributions in the Moldovan cohort further emphasize population-specific immunogenetic characteristics, distinguishing it from Mediterranean and other European groups.

Author contributions

E.R., M.B., V.C., and L.G. conceived and designed the study. E.R., M.B., V.C. and L.C. performed data analysis and interpretation. E.R. and V.C. drafted the manuscript. All authors critically revised the manuscript for intellectual content, approved the final version, and agreed to be accountable for all aspects of the work.

Compliance with Ethics Requirements:

"The authors declare no conflict of interest regarding this article"

"The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008 (5), as well as the national law. Informed consent was obtained from the patients included in the study."

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