Unveiling the Link: HLA-B27 Genetic Marker and Interleukin Levels in Psoriatic Arthritis Patients

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Abstract

This study aimed to examine the occurrence of Human leukocyte antigen-B27 (HLA-B27) and its subtypes, alongside the levels of the inflammatory markers Interleukin-17 and Interleukin-23 in individuals diagnosed with psoriatic arthritis (PsA), a multifaceted, polygenic disorder strongly influenced by genetic factors. An observational cross-sectional study was carried out that included patients who satisfied the CASPAR criteria for Psoriatic arthritis. This study revealed a male predominance among PsA patients and an association between HLA-B27 positivity and an earlier age of onset.

Notably, theHLA-B27 subtypes B27:05, B27:04 and HLA-B27:02, B27:07 were not detected in any HLA-B27 positive Psoriatic arthritis patients in our study. Additionally, elevated levels of Interleukin-17 and Interleukin-23 were observed, particularly in Human leukocyte antigen-B27 positive PsA patients.

Keywords: Psoriatic arthritis, HLA-B27, Interleukin-17, Interleukin-23.

Introduction

Psoriatic arthritis (PsA) is a complex, polygenic disorder with a significant heritability factor. Notably, it poses a notably greater recurrence risk than both Rheumatoid arthritis (RA) and psoriasis. Recurrence risk, which indicates the ratio of clinical presentation among family members to its occurrence in the broader populace, serves as a crucial marker of its heritability. In contrast to rheumatoid arthritis (RA), which shows established associations with certain MHC class II alleles, psoriasis and PsA are linked to MHC class I alleles, with the most prominent genetic factor associated with psoriasis[3].

While psoriatic arthritis is most frequently diagnosed in individuals aged 40 to 50 years, it can affect people of all age groups including children and the elderly individuals. Psoriasis vulgarise is the most prevalent type of psoriasis associated with PsA, with a small percentage of individuals (4% to 5%) exhibiting guttate and pustular psoriasis.

Isolated nail involvement without skin symptoms occurs in 1% to 2% of cases. The male-to-female ratio varies between 0.7 and 2.1:1[1]. Approximately 10% to 37% of individual's experience concurrent skin and joint involvement where as 6% to 18% of patients develop arthritis before psoriasis.

Globally, the prevalence of PsA varies significantly. In Japan, it ranges from 0.1/100,000 to 23.1/100,000, whereas in Europe and America, it ranges from 0.02 percent to 0.42 percent. Notably, within Singapore's diverse multiethnic population, those with Indian ancestry present the highest PsA prevalence. Comparatively, Asia, as a whole, generally displays lower incidence and prevalence rates of PsA than the combined figures for the Americas and Europe[8,27,28].

The severity of psoriatic arthritis is correlated with increased mortality rates and increased joint damage. Patients with PsA have an elevated risk of death, as indicated by a standardized mortality ratio of 1.62. The primary causes of death in psoriatic arthritis patients mirror those in the general population, with cardiovascular diseases being the most common. The presence of erosive disease, the extent of required treatment and history of active and severe disease all contribute to an increased risk of premature fatality[11,26].

Research has highlighted a correlation between the presence of HLA-B27 and the severity of axial involvement in MRI studies[4]. Furthermore, elevated levels of Interleukin-23p/Interleukin-23R and Interleukin-17/Interleukin-17R have been observed in the synovial fluid and psoriatic skin of PsA patients, highlighting the importance of the interleukin-23/interleukin-17 axis in PsA. Studies by Leipe et al[15] underscored the contribution of CD4+ IL-17 cells to inflammation in both rheumatoid and psoriatic joints.

Psoriatic arthritis (PsA) is a complex inflammatory condition characterized by a combination of psoriasis and arthritis symptoms. As part of the spondyloarthritis (SpA) group, it can significantly impact a patient's quality of life because of its chronic and often debilitating nature. Understanding the prevalence, genetic markers and inflammatory profiles associated with PsA is crucial for improving diagnostic accuracy and treatment strategies.

This study aimed to investigate the correlation between interleukin-17 (IL-17) and interleukin-23 (IL-23) levels and HLA-B27 and its subtypes in PsA patients. This study provides significant insights into the epidemiology and clinical characteristics of PsA among spondyloarthritis patients in a specific demographic region of Tamil Nadu, India. By enrolling 289 patients who met the CASPAR criteria for PsA and conducting comprehensive genetic and

inflammatory marker analyses, this research highlights several key findings. Additionally, that study sought to ascertain the prevalence of the HLA-B27 antigen and its subtypes in PsA while assessing their associations with IL-17 and IL-23 levels.

Material and Methods

Study design and participants: This study employed a cross-sectional observational design. Participants who met the CASPAR criteria for psoriatic arthritis (PsA) were enrolled. These individuals had attended the dermatology and rheumatology clinics at SRM Medical College Hospital and Research Centre in Potheri, Tamil Nadu, India, between August 2017 and January 2021. Individuals diagnosed with other autoimmune diseases, including systemic lupus erythematosus (SLE), rheumatoid arthritis and polymyalgia rheumatica, were excluded. Informed consent was obtained from all participants prior to their inclusion in the study. The sample size was determined via the computational formula $4pq/L^2$, which is based on the prevalence of spondyloarthritis, resulting in the enrollment of a total of 289 patients.

Identification of the Genetic Marker HLA-B27

Blood sample collection and DNA extraction: Blood samples were collected from eligible patients via EDTA tubes following standard protocols. DNA was extracted via the Trueprep® AUTO/AUTO v2 Universal Cartridge-based Sample Prep Device and kit. The patient's ID was attached to the Truenat™ HLA-B27 chip and purified DNA was applied.

RT-PCR for HLA-B27 detection: The presence of HLA-B27 was identified via real time polymerase chain reaction (RT-PCR). The test run generated results indicating the presence or absence of HLA-B27, including the threshold cycle (Ct) value of the Internal Positive Control (IPC).

HLA-B27subtype: HLA-B27 subtyping was performed via the Illumina dye sequencing technique, which involves three main steps: amplification, sequencing and data analysis. This technique uses a four-color DNA sequencing-by-synthesis method with reversible terminators and high sensitivity fluorescence detection.

Sample Processing and DNA Extraction

1. **For sample processing**: 500 µL of the blood sample was mixed with lysis buffer and allowed to react for 3 minutes.
2. **Extraction**: The processed sample was loaded into a cartridge and placed in the Trueprep AUTO device. The automated process was initiated and the eluted DNA was collected for analysis.

Chip-based RT-PCR: The HLA-B27 chip was loaded into the analyzer and 6 µL of the purified DNA was added. The RT-PCR test was executed and the results are displayed as either "DETECTED" or "NOT DETECTED," on the basis of the Ct value.

Illumina Dye Sequencing for HLA-B27 Sub-tying:

1. **Amplification**: Fragmented genomic DNA was attached to a planar surface on a flow cell.
2. **Sequencing**: Sequencing was performed via reversible terminators with removable fluorescence. This process involved:

a. High sensitivity fluorescence detection.
b. Sequencing-by-synthesis to generate the base sequences.

3. **Data analysis**: The sequenced data were analyzed to determine the specific subtypes of HLA-B27.

This comprehensive methodology ensures accurate detection and sub-typing of HLA-B27, providing valuable insights into the genetic markers associated with psoriatic arthritis in the study population.

Performing ELISA Test

Sample Preparation: Blood samples were collected from the patient population after providing consent. The blood was collected in plain vacutainer tubes and allowed to clot at room temperature. The samples were then centrifuged at 3000 rpm for 10 minutes to separate the serum which was used for testing.

ELISA Procedure: Interleukin-17 (IL-17) and interleukin-23 (IL-23) levels were measured via Elabscience Human-IL17 and Human-IL23 Sandwich ELISA kits. The following steps were performed according to the kit protocols.

1. **Preparation:** All reagents and materials were brought to room temperature. Wash solutions and standard working solutions were prepared as directed.
2. **Standard and Sample Addition:** 100 µL of different standard solutions and test serum were added to the wells.
3. **For incubation:** The plates were incubated for 90 minutes at 37°C.
4. **Antibody addition:** 100 µL of biotinylated detection antibody working solution was added and the mixture was incubated for 1 hour at 37°C.
5. **Washing**: Wells were washed multiple times with wash buffer.
6. **HRP Conjugate addition:** 100 µL of HRP conjugate working solution was added and the mixture was incubated for 30 minutes at 37°C.
7. **Substrate addition**: 90 µL of substrate reagent was added and the plates were incubated for 15 minutes at 37°C in the dark.
8. **Stopping Reaction:** The reaction was stopped by adding 50 µL of stop solution to each well.
9. **Optical density measurement:** The optical density (OD) was measured at 450 nm using a micro plate reader.

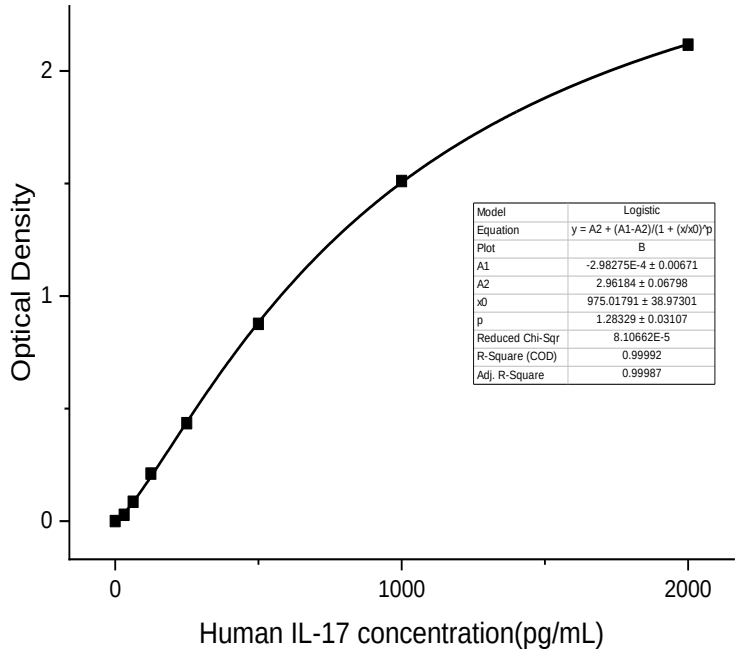
Result Calculation: The duplicate readings for each standard and sample were averaged and the zero standard OD was subtracted. A four-parameter logistic curve was plotted on log-log graph paper. The concentration was calculated on the basis of this curve and was adjusted for any dilution factors.

Results

Among the 289 spondyloarthritis patients,10.7% (31/289) were confirmed to have psoriatic arthritis by a dermatologist. Among these, 77.4% (24/31) were male and 22.6% (7/31) were female, resulting in a male: female ratio of 3.4:1. For data analysis, patients were categorized into five distinct age brackets (Table 3). The highest number of patients in the 16 to 25-year age bracket was male, whereas in the 36 to 45-year age bracket, the majority were female. Among the 31 PsA patients, 61% (19/31) were HLA-B27 positive, with 89% (17/19) male and 11% (2/19) female. The frequency of HLA-B27 subtypes by sex is detailed in fig. 1.

Table 1
Standard concentration (OD) values of IL-17

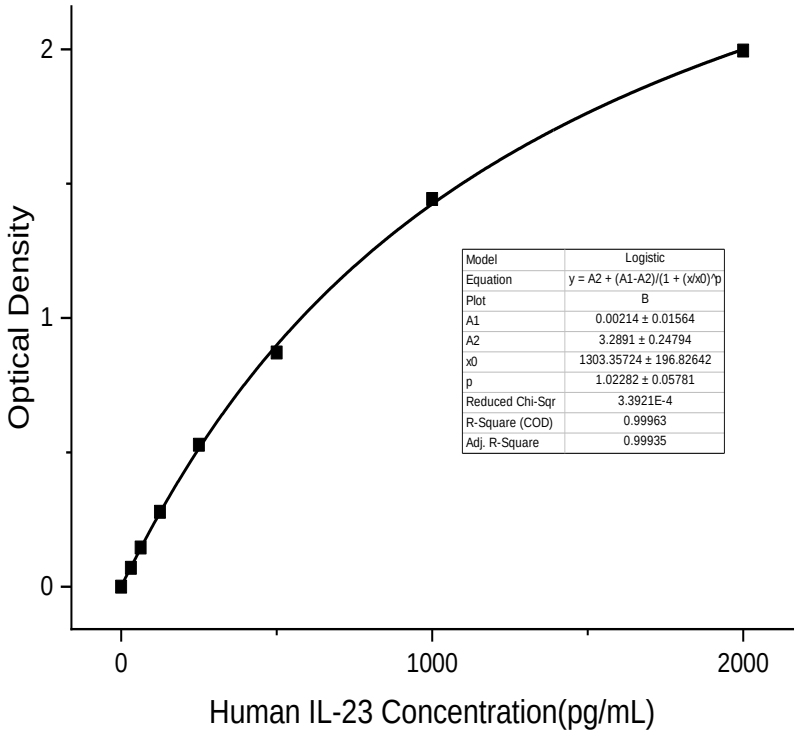
Concentration (pg/mL)	Std-OD1	Std-OD2	mean OD	Corrected OD
2000	2.143	2.11	2.126	2.106
1000	1.66	1.386	1.523	1.503
500	0.928	0.846	0.887	0.867
250	0.512	0.391	0.451	0.431
125	0.215	0.242	0.228	0.208
62.5	0.104	0.106	0.105	0.085
31.25	0.048	0.048	0.048	0.028
0	0.019	0.022	0.02	0



Graph 1: IL-17 Standard concentration calculation graph

Table 2
Standard concentration (OD)values of IL-23

Concentration (pg/mL)	Std-OD1	Std-OD2	mean OD	Corrected OD
2000	2.133	2.091	2.112	1.995
1000	1.584	1.536	1.56	1.443
500	1.065	0.912	0.9885	0.8715
250	0.643	0.648	0.6455	0.5285
125	0.439	0.352	0.3955	0.2785
62.5	0.254	0.271	0.2625	0.1455
31.25	0.192	0.182	0.187	0.07
0	0.136	0.098	0.117	0



Graph 2: IL-23 standard concentration calculation graph

Table 3
Allocation of Psoriatic Arthritis Patients Based on Age and Gender with the Status of Genetic Markers

Age	Men		Women	
	HLA-B27 Positive	**HLA-B27 Negative**	**HLA-B27 Positive**	**HLA-B27 Negative**
16-25	12	1	0	2
26-35	3	0	0	1
36-45	0	2	1	2
46-55	0	0	0	0
>56	2	4	1	0
Total	**17**	**7**	**2**	**5**

HLA-B27 subtype B27:05 was the most common subtype, followed by B27:04, whereas HLA-B27:02 and B27:07 were not detected in any HLA-B27 positive psoriatic arthritis patients in our study.

The levels of the inflammatory markers IL-17 and IL-23 were elevated in 63% (12/19) of the patients within the 16 to 25 age bracket and in 33% of the patients over the age of 30. In HLA-B27-negative PsA patients, 37% of individuals aged 16 to 25 years presented increased levels of the inflammatory markers interleukin-17 and interleukin-23, with reference values of IL-17 in healthy human serum ranging from 3 -30.5 pg/mL and IL-23 from 5 - 95.3 pg/mL per kit (Fig. 2). Notably, among patients who were HLA-B27 positive, 11% were human leukocyte antigen-B27 positive but did not exhibit elevated inflammatory markers.

In our study of 289 spondyloarthritis patients, psoriatic arthritis symptoms were observed in 11% (31/289) of the individuals. The majority of patients, accounting for 38% (12/31), reported mild pain, whereas 13% (4/31) experienced the worst pain (Table 4). Clinical symptoms, such as swollen fingers with redness, were noted in 65% (20/31) of the patients, with a male predominance of 80% (16/20). Additionally, 52% (16/31) of patients reported low back pain, 48% (15/31) experienced nail discoloration and 39% (12/31) experienced morning stiffness.

Other symptoms included scaly skin (35%, 11/31), food pain (32%, 10/31), swollen toes (29%, 9/31), fatigue (26%, 8/31) and red eyes (6%, 2/31), with females predominantly affected in the latter (100%) (Table 5). Furthermore, psoriatic arthritis symptoms were prominently observed in the 16 to 25-years-old male group, whereas females aged 36 to 45 years, specifically HLA-B27- positive patients, presented a greater prevalence (Table 6).

Discussion

Psoriatic arthritis arises from a complex interplay of hereditary and environmental factors. The global incidence

of this condition varies, ranging from 6.25% to 48% in regions such as Europe, North America and South Africa whereas the prevalence's are lower in Asian countries, typically falling within the range of 1% to 9% among psoriatic patients[9,15,16,18,19,23]. In our study, the prevalence was 10.7% among spondyloarthritis patients, which aligns with the prevalence observed in numerous Asian countries. While most studies suggest an equal sex distribution for psoriatic arthritis, our findings, which are consistent with those of a study from Pondicherry, India, indicate a higher prevalence in a male-predominant population with men comprising 24/31 and women comprising 7/31 PsA cases[5,13,22,24,25].

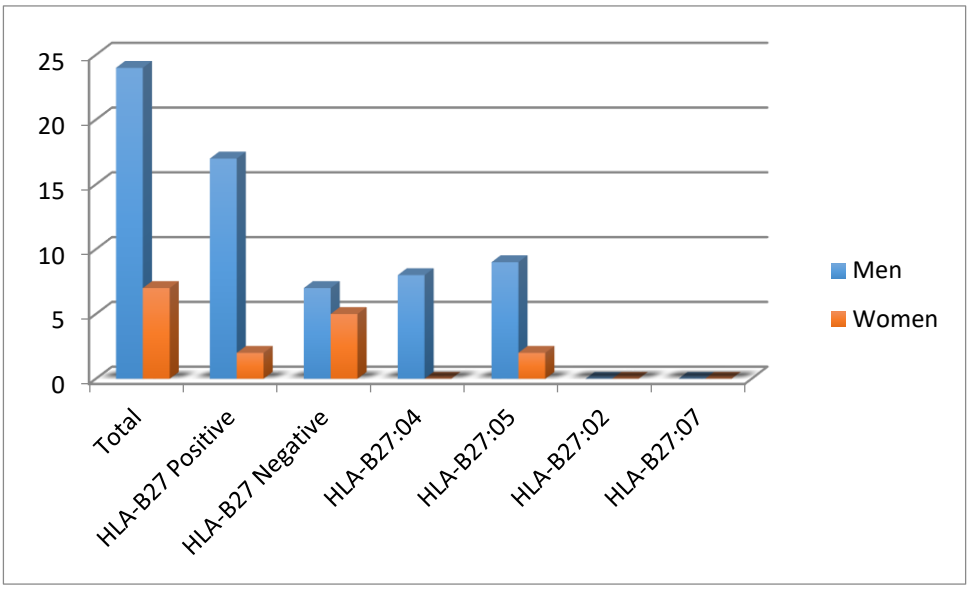


Figure 1: Frequency of Human Leukocyte Antigen-B27 and Sub-types present in Psoriatic Arthritis.

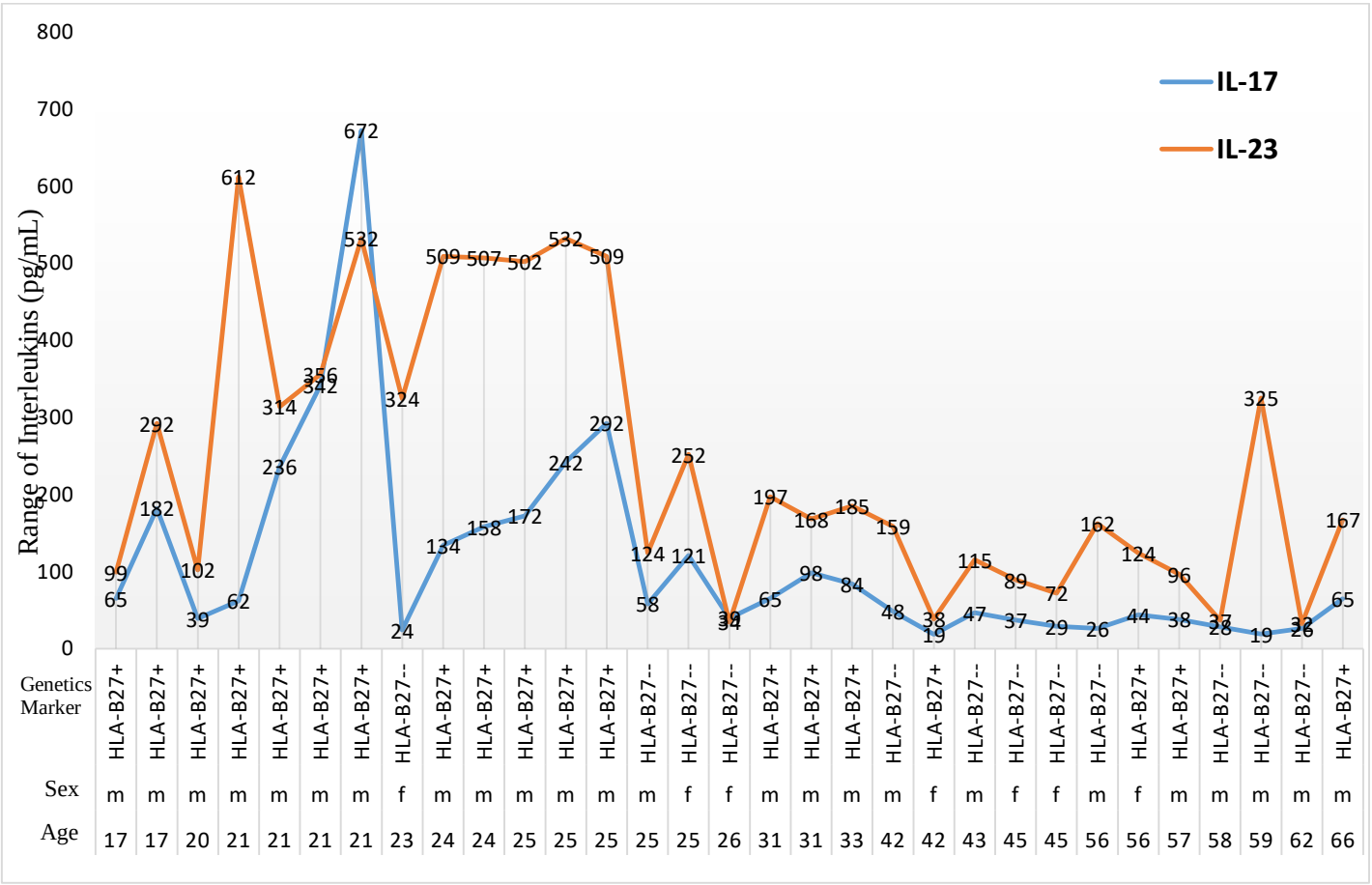


Figure 2: Correlation between heightened Interleukins and HLA-B27 positive individuals categorized by age and gender

Table 4
Psoriatic Arthritis Clinical Presentation Correlated with Genetic Marker (All Values in Percentage)

Symptoms	HLA-B27 Positive		HLA-B27 Negative	
	Men	Women	Men	Women
Swollen finger with redness	80	5	15	0
Low back Pain	19	6	44	31
Nail discoloration	27	13	27	33
Morning stiffness	25	17	33	25
Scaly skin	64	0	27	9
Foot pain	50	0	30	20
Swollen toes	78	0	0	22
Fatigue	25	13	62	0
Redness eye with pain	0	100	0	0

Table 5
Psoriatic Arthritis Clinical Presentation Correlated with Age and Gender Distribution (All Values in Percentage)

Clinical Presentation	Total	16-25yrs		26-35yrs		36-45yrs		46-55yrs		>56yrs	
		Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
Swollen finger	65	55	0	15	0	5	5	0	0	15	5
Low back Pain	52	25	13	0	6	13	13	0	0	25	5
Nail discoloration	48	13	13	0	7	13	20	0	0	27	7
Morning stiffness	39	18	8	0	0	8	25	0	0	33	8
Scaly skin	35	37	0	9	0	9	9	0	0	36	0
Foot pain	32	50	10	10	0	10	10	0	0	10	0
Swollen toes	29	56	0	11	11	0	11	0	0	0	11
Fatigue	26	0	0	0	0	13	13	0	0	75	0
Redness eye with pain	6	0	0	0	0	0	50	0	0	0	50

Table 6
Psoriatic Arthritis Pain Recorded on Visual Analog Scale (VAS Score) (All Values in Percentage)

Clinical Presentation	16-25yrs		26-35yrs		36-45yrs		46-55yrs		>56yrs	
	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
No Pain	0	0	0	0	0	0	0	0	0	0
Mild pain	0	0	0	8	17	25	0	0	8	42
Moderate pain	37	25	25	0	0	0	0	0	13	0
Severe pain	75	0	25	0	0	0	0	0	0	0
Very severe pain	100	0	0	0	0	0	0	0	0	0
Worst pain	100	0	0	0	0	0	0	0	0	0

In study by Parasannanavar et al[20], we observed that the clinical manifestation of psoriatic arthritis typically commenced between the ages of 30 and 50 years. Among the psoriatic arthritis patients who tested negative for HLA-B27, 67% were over 30 years old whereas 33% were between 16 and 25 years old. Conversely, among those who tested positive for HLA-B27, the majority of psoriatic arthritis patients (63%) were in the age range of 16 - 25 years, with 37% being over 30 years[6,7].

Between 1991 and 2001, in Chennai, Rajendran et al[21] conducted a study on psoriatic arthritis, revealing that knee joint involvement was observed in 66.4% of cases. In our study, 65% of the participants presented swollen fingers with redness and eye manifestations were present in 1.7% of the patients. Notably, Mithun et al[18] reported a 1% incidence in Pondicherry in 2013, whereas our study reported a significantly higher rate of 6%, particularly among HLA-B27-positive female patients aged >40 years. Furthermore, nail involvement was observed in 17.7% of our patients, representing a substantial increase compared with the 48% reported in previous studies[14,17].

The evaluation of the inflammatory markers IL-17 and IL-23 revealed significant associations with psoriatic arthritis (PsA). Elevated ranges of interleukin-17 and interleukin -23 were observed in a substantial proportion of PsA patients, particularly those in the 16−25 years age group. Moreover, in HLA-B27 negative PsA patients, a notable percentage exhibited increased ranges of interleukin -17 and interleukin -23, emphasizing the potential role of these inflammatory markers as crucial indicators of disease activity and progression, independent of HLA-B27 status[2,29].

Research consistently indicated increased concentrations of interleukin-17 in the synovial fluid and serum of PsA patients[12]. Furthermore, Interleukin-17 plays a crucial role in the process of bone resorption and RANKL-mediated osteoclastogenesis, suggesting that inhibiting IL-17 signalling may provide dual benefits by reducing systemic inflammation and mitigating joint damage in individuals with PsA[20].

Conclusion

This research provides valuable insights into the genetic and immunological aspects of psoriatic arthritis. The observed male predominance in our PsA patient cohort is in line with previous studies, shedding light on potential sex-specific factors contributing to the development of this condition. It was discovered that HLA-B27, particularly subtypes B27:05 and B27:04, was associated with PsA, suggesting that it may be a genetic marker.

Furthermore, the significance of the IL-23/IL-17 axis in the pathophysiology of psoriatic arthritis is highlighted by the higher levels of IL-17 and IL-23 in patients with psoriatic arthritis, especially those who test positive for HLA-B27. These findings increase our understanding of psoriatic arthritis and can potentially guide future research in the development of targeted therapies for this debilitating condition.

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