

Correlation of Interleukin-17 and 23 Inflammatory Markers with Genetically Transmitted Spondyloarthritis Patients at a Tertiary Care Facility, South India

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Abstract

Human leukocyte antigens (HLA) are genetically derived proteins in the major histocompatibility complex. They help distinguish “self” and “non-self” antigens and are essential in interacting with the immune cells inside the body. The present research work examines the prevalence of HLA-B27 among patients suspected of Spondyloarthritis (SpA), which has also been correlated with Interleukin-17/23 Inflammatory Markers and other clinical manifestations and was carried out between August 2017 to January 2021. The patient’s blood samples were collected and tested for HLA-B27 and Interleukin-17/23 inflammatory markers. Among 289 SpA patients, 60% (172) were males, and 40% (117) were females, with a ratio of 1.5:1. Ankylosing Spondylitis (65.1%) was found to be the most prevalent subgroup of SpA among the patients, closely followed by reactive arthritis (21%), psoriatic arthritis (10.7%), undifferentiated spondyloarthritis (2.1%), and inflammatory bowel disease with associated arthritis (1%). HLA-B27 was found to be positive in 54% (156) out of 289 patients. Normal IL-17 ranges were seen in 42% of HLA-B27- positive patients, while increased IL-17 was seen in 58% of the population with positive HLA-B27 cases. IL-23 was found within normal ranges in 40% of positive HLA-B27 cases, while it was found to be increased in 60% of the positive HLA-B27 positive subjects. We concluded that HLA-B27 was found to be positive among more than half of the patient population with SpA. The early detection of HLA-B27 may aid in changing lifestyle to prevent Spondyloarthritis.

Keywords: Spondyloarthritis, HLA-B27, Inflammatory Markers, Reactive Arthritis

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Citation: Jayaprakash T, Leela KV, Venkatesan B, Ravi S, Muthamilan OL. Correlation of Interleukin-17 and 23 Inflammatory Markers with Genetically Transmitted Spondyloarthritis Patients at a Tertiary Care Facility, South India. *J Pure Appl Microbiol.* 2023;17(2):1038-1046. doi: 10.22207/JPAM.17.2.33

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INTRODUCTION

Spondyloarthritis (SpA) is a subset of inflammatory arthritis with a significant genetic correlation to class I HLA antigens with clinical manifestations and etiological variations.^{1,3} This group of illnesses usually affects the sacroiliac (SI) joints, and they are distinguished by their axial involvement and lack of rheumatoid factor.⁴ SpA also prefers to affect the body's key joints, and along the length of the spine, it produces pain, stiffness, and twinging (*suffer a sudden, sharp localized pain*). Inflammatory arthritis with coincidental characteristics among clinical manifestations sub-groups of SpA involves Psoriatic arthritis (PsA), Ankylosing spondylitis (AS), Juvenile onset Spondyloarthritis (JOSpA), Undifferentiated Spondyloarthritis (uSpA) and Reactive arthritis (ReA) correlated with spondylitis and Inflammatory bowel disease (IBD). The prevalence of males over women for this condition (ranges from 2.6:1 to 5:1) is higher in the second or third decade, and the immediate relations of affected individuals have a 12% prevalence of SpA.^{5,6} The most prevalent subgroup of SpA is ankylosing spondylitis, and it has a high relationship with HLA-B27, which has been noted in various research for more than 30 years. Several investigations have also demonstrated the infective significance of the gene B27 from the onset of AS.^{6,7}

Identification of HLA-B27 has been considered a genetic marker that significantly aids in detecting illness.⁸⁻¹⁰ The correlation between ankylosing spondylitis and HLA B27 was initially noted in 1973¹¹ and subsequently proven to be connected to different forms of spondyloarthritis by many researchers.¹² Moreover, having a solid interrelation with AS and spondyloarthritis, HLA-B27 is critical to the pathophysiology of the illness. HLA-B27 is present in 88–90% of AS patients, although in 4-8% of the average population.¹³⁻¹⁵ Among seronegative spondyloarthritis (SSpA) patients, the association of HLA-B27 ranges from 19% to 94%, while it is between 1.4% and 8% in the general population in India.¹⁶⁻¹⁸ B*27:05 and B*27:04 were the two SpA subtypes most often seen among South Indians.¹⁹⁻²¹ HLA-B27 homodimers promote the signaling pathway of IL-17/IL-23 and inflammation through two different mechanisms, which involve

the enhancement of the production levels of Th17 cells, which results in IL-17/IL-23 production,²² and HLA-B27 homodimers binding with leukocyte immunoglobulin-like receptors (LILRs) as they were demonstrated upon T cells as well as NKs by promoting the IL-23/IL-17 signaling.²³ The interaction of KIR3DL2 with HLA-B27 homodimers has also been shown to aid CD4+ T cell survival and differentiation in SpA patients. Furthermore, it boosted pro-inflammatory cytokine production, such as IFN-gamma, IL-17, and TNF.²⁴ Moreover, CD4+ T-cells and KIR3DL2+ NK cells are more abundant among positive HLA-B27 SpA patients' peripheral blood, with higher levels of IL-17 cytotoxicity overnegative HLA-B27 SpA patients.^{25,26} This research aims to determine the frequency of HLA-B27 antigen present in spondyloarthritis association with Interleukin-17/23 Inflammatory Markers.

MATERIALS AND METHODS

This cross-sectional observational research was held from August 2017 to January 2021 at a tertiary care facility, SRM Medical College Hospital and Research Centre, Kattankulathur. Patients who had met the criteria of Assessment of Spondyloarthritis International Society for spondyloarthritis (ASAS) and visited the rheumatology clinic were included with their proper consent, and patients having additional autoimmune illnesses, like polymyalgia rheumatica, rheumatoid arthritis and systemic lupus erythematosus (SLE) were excluded from the research. Blood samples were collected aseptically by the standard protocol with the trained phlebotomist.

The genetic marker HLA-B27 has been identified by using a Chip based Real-Time PCR (RT-PCR) technology. These results were shown on the Truelab® analyzer screen along with the validation; HLA-B27 was "DETECTED" or "NOT DETECTED" and the threshold cycle value (Ct value) of the internal positive control (IPC). A human-Interleukin-17/23 Inflammatory Markers Enzyme-Linked Immunosorbent Assay (ELISA) kit was commercially available at Elabscience, India. As per the manufacturer protocol, ELISA procedures were done, and the optical density (OD) was measured spectrophotometrically.

RESULTS

As per ASAS criteria, 289 patients were selected in a ratio of 1.5:1 (Men and women). Ankylosing spondylitis (AS) occurs as one of the predominant sub-group within the patients, accounting for 188(65.1%) of them. The frequency of the additional SpA sub-groups is given in (Table 1). HLA-B27 positivity was identified in 156(54%) of the study population of SpA. Of

them, Men were predominantly positive 100(64%) compared to women 56(36%). The sub-types of HLA-B27:04(35%), and HLA-B27:05(27%) are highly distributed among men in the study population. HLA-B27:04 had the highest prevalence, 83(53%), among the total study population. HLA-B27:07 was equally distributed among men and women (Figure 1).

Among the total study populations, clinical manifestations were recorded as 185(64%) of knee

Table 1. Distribution of SpA patients by age groups, gender and SpA groups

SpA group classification		AS	ReA	PsA	uSpA	IBD	TOTAL
Age group with Gender	16-25 M	13	33	13	-	-	59
	16-25 F	5	7	2	-	1	15
	26-35 M	35	12	3	2	1	53
	26-35 F	25	2	1	-	-	28
	36-45 M	31	6	2	1	1	41
	36-45 F	42	1	3	-	-	46
	46-55 M	9	-	-	-	-	9
	46-55 F	17	-	-	2	-	19
>56	M	4	-	6	1	-	11
	F	7	-	1	-	-	8
TOTAL		188	61	31	6	3	289

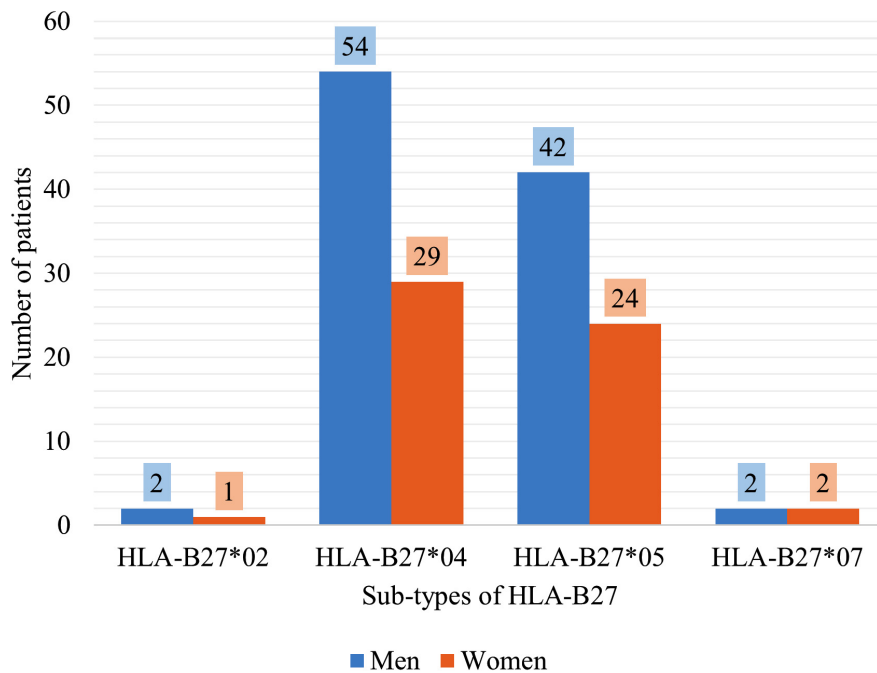


Figure 1. Distribution of sub-types among HLA-B27 positive SpA patients

joint pain, followed by lower back pain 101(35%), and neck pain 66(23%) were the most common clinical manifestations seen. The positivity among HLA-B27 was less reported amongst patients presenting with lower back pain 37(36.6%) and knee pain 86(46.4%), while positivity of HLA-B27 has been increased among patients presenting with other articular manifestations (Figure 2). Extra-articular expressions like Uveitis have affected 15 individuals with HLA-B27 positivity, while 19 patients had skin rashes, which comprise the majority of extra-articular symptoms.

The association of IL-17 was found to be normal in 33(21%) of HLA-B27 positive subjects, compared with the reference range (3-30pg/mL), while increased in 123(79%) of the HLA-B27 positive patient population, with a significant p-value of 0.001. IL-23 was found within normal ranges in 37(24%) with a reference range (5-95.3pg/mL) of the HLA-B27 positive patient group,

whereas it was found to be increased in 119(76%) with a significant p-value of 0.001. IL-17 was found to be raised in 31.1% of HLA-B27*04 patients, which was reported as the highest, followed by 24.5% in HLA-B27*05 patients. Increased IL-23 ranges were found in 31.5% and 26.9% in HLA-B27:04 and HLA-B27:05. p-value(0.01) was found to be significant (Figure 3), and <35% of patients were within the normal range among all subgroups except in uSpA and SpA IBD. Increased IL-17 ranges were seen exceedingly among uSpA (100%), and ReA (80%) patients, while increased IL-23 ranges were seen mostly among PsA (81%), and ReA (79%) patients (Table 2).

The pain caused in axial and peripheral arthritis in SpA patients is measured using a visual analog scale (VAS) by a rheumatologist. The VAS consists of a straight line with the endpoints defining extreme limited such as no pain at all and pain as bad. The patient is asked to mark his pain

Table 2. Association of normal and abnormal levels of inflammatory markers with subgroups of Spondyloarthritides

Markers	AS	ReA	PsA	UnSpA	IBD
IL-17 Normal	55(29%)	12(20%)	7(23%)	0(0%)	3(50%)
IL-17 Increased	133(71%)	49(80%)	24(77%)	3(100%)	3(50%)
IL-23 Normal	68(36%)	13(21%)	6(19%)	2(67%)	3(50%)
IL-23 Increased	120(64%)	48(79%)	25(81%)	1(33%)	3(50%)

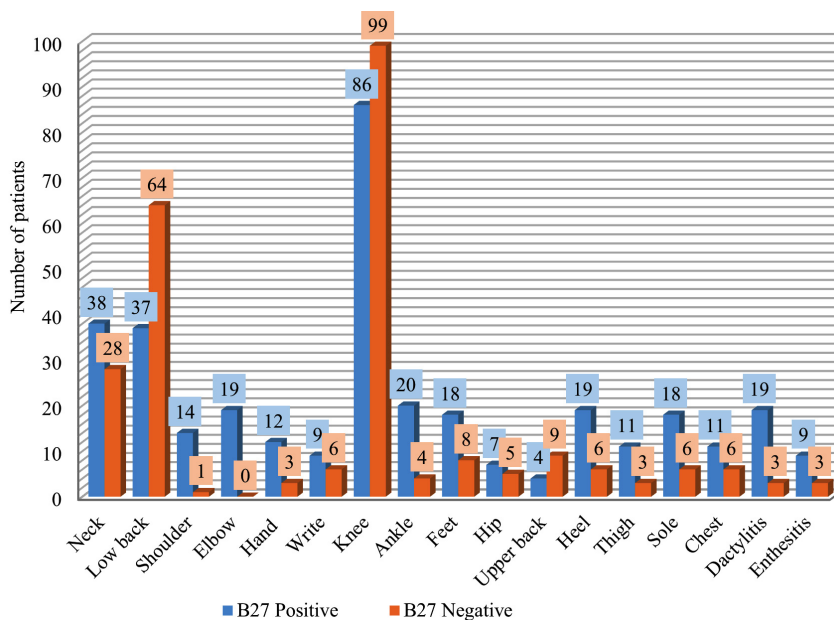


Figure 2. Distribution of clinical manifestations correlated with HLA-B27 positivity among SpA patients

level on the line between the marks on the line between the two endpoints.

Moderate pain was increasingly reported in patients with increased IL-17(32.5%) compared to patients with normal IL-17 values(13%). Very severe pain and Worst pain were reported in 7% and 2.4% of patients with raised IL-17 values, respectively. p-value was found to be significant (0.001). Mild pain(41%) was the most commonly reported pain score in patients with increased IL-23, which was closely followed by an average pain score (35%). A similar trend was seen among patients with normal IL-23 ranges, with most of the patients with mild pain scores (88%). p-value was found to be significant (0.001). All of the patients with very severe pain and worst pain scores had increased IL-23 levels. Similarly, 96.6% of patients with severe pain scores had increased levels of

IL-23. (Figure 4). The gender-wise distribution of various ranges of IL17 and IL23 were shown in (Tables 3 and 4), and pain score was correlated with HLA-B27 positive along with Interleukin-17 and 23 (Table 5).

DISCUSSION

The pathophysiology of autoimmune illnesses can be influenced by an array of pro-inflammatory cytokines and chemokines.²⁷ The study regarding the correlations between IL-17 and IL-23 has some contradictions. Th17, the cell source of IL-17, has recently been identified as a novel subset of T cells that is soon to have a role in the pathogenesis of an assortment of autoimmune diseases.²⁸ Recent research has shown that IL-23 plays a critical pathogenic

Table 3. Distribution of IL17 ranges in Men and Women

Value (pg/mL)	<30.5	31-100	101-200	201-300	301-400	401-500	501-600	601-700
Men	33	85	27	16	10	1	1	8
Women	44	48	10	5	0	0	0	1
Total	77	133	37	21	10	1	1	9

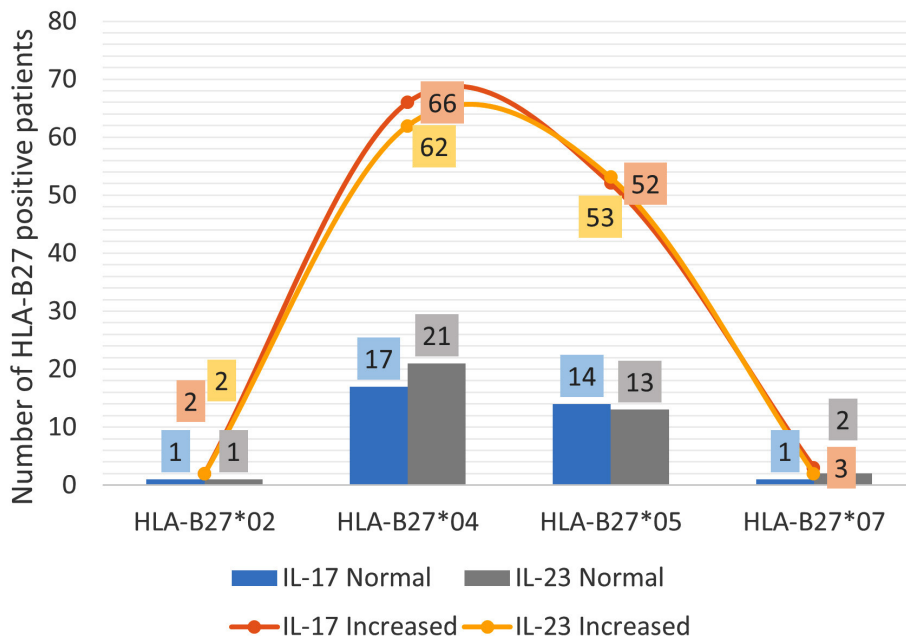


Figure 3. Association of HLA-B27 subtypes with normal and abnormal values of IL-17 and IL-23 among HLA-B27 positive patients

role in developing autoimmunity and chronic inflammation in many autoimmune disease models, including experimental inflammatory arthritis and experimental colitis.²⁹

IL23 is a heterodimeric cytokine comprising a p40 subunit that it shares with a p19 subunit and IL12. The IL-17 family consists of

IL-17A, IL-17B, IL-17C, IL-17D, IL-17E and IL-17F. In the current investigation, we observed that Spondyloarthritis serum levels of IL-17 and IL-23 were considerably higher than those of healthy controls.²⁹ These results accord with the study findings of Romero-Sanchez C et al.³⁰ Additionally, Spondyloarthritis patients had considerably greater

Table 4. Distribution of IL23 ranges in Men and Women

Value (pg/mL)	<95.3	96-100	101-200	201-300	301-400	401-500	501-600	601-700	700-800
Men	33	22	55	16	10	4	14	14	4
Women	59	14	25	10	5	4	0	0	0
Total	92	36	80	26	15	8	14	14	4

Table 5. Distribution of pain score correlated with Interleukins value in HLA-B27 positive SpA patients

HLA-B27 Positive + Inflammation	Mild Pain	Moderate Pain	Severe Pain	Very Severe Pain	Worst	Total
HLA-B27+IL-17 Increased	35(23%)	45(29%)	24(15%)	14(9%)	5(3%)	123
HLA-B27+IL-17 Normal	27(17%)	5(3%)	1(1%)	0(0%)	0(0%)	33
HLA-B27+IL-23 Increased	32(21%)	44(28%)	24(15%)	14(9%)	5(3%)	119
HLA-B27+IL-23 Normal	30(19%)	6(4%)	1(1%)	0(0%)	0(0%)	37

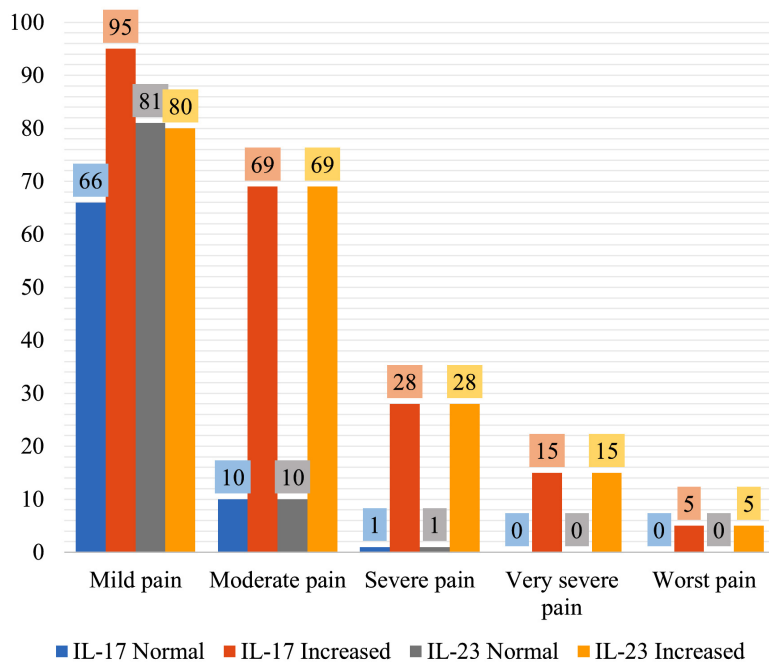


Figure 4. Distribution of normal and abnormal ranges of IL-17 and IL-23 among SpA patients in association with their respective pain scores

serum levels of IL-23 than healthy controls, while there was no difference in IL-17 levels between Spondyloarthritis patients and healthy controls, as reported by Milanez et al.³¹ While Deveci et al.³² Showed a decrease of these cytokines in AS patients compared to healthy controls; Sveas et al. reported no significant change in serum IL-17 and IL-23 levels. Our data showed that serum IL-17 and IL-23 levels were significantly higher in HLA-B27 positive SpA patients compared with age- and gender.

Our research further assessed the relationships between these cytokine levels and distinctive disease-related variables, including disease activity, function, mobility, enthesitis index, therapeutic agents, and quality of life pain. The current investigation also had a significant association between the serum IL-23 and IL 17 levels with pain. However, IL-23 and other disease-related characteristics did not significantly correlate. Melis et al.³³ also reported that systemic levels of IL-23 are strongly associated with disease activity in RA but not SpA. In a study conducted by Chen et al., it was reported that the serum IL-17 and IL-23 levels were associated with pain scores but not with capacity for the functioning or spinal mobility among patients with AS.

HLA-B27 has a long history of being strongly genetically linked to AS.^{34,35} In our investigation, HLA-B27 was shown as frequently linked to AS (62.8%) than to ReA (21.2%) or PsA (12.2%), similar results stated by Kamal et al.² that HLA B27 mainly was related to AS (69%). After rheumatoid arthritis, the second most prevalent inflammatory arthritis in India is spondyloarthritis. With a predominance of men, 54% of patients with spondyloarthritis tested positive for the particular genetic marker HLA-B27. HLA-B27 positivity was noticed in 26% of the 50 patients studied by Uma Maheshwari et al.,³⁶ while additional investigations of Mishra MN et al.³⁷ and Nessa et al.³⁸ indicated that HLA-B27 antigen was present in 49.2% and 56% of SpA patients, respectively.

Comparing men and women with SpA patients, it was observed that more males (64%) than women (36%) had HLA-B27 positivity, which is consistent with other research findings.^{36,38} However, Vaidya et al.³ stated that there was no significant difference was noticed in HLA-B27 incidence between women and men, and it was

found that the illness was more common in the male population.

Although, HLA-B27 was shown to be more often in SpA patients. Ankylosing spondylitis was reported as the highest prevailing clinical manifestation (65.1%), while UuSpA had the lowest prevalence (2.1%), and one incidence of inflammatory bowel disease (IBD) was observed. From the study results of Kamal et al.,² it was found that psoriatic arthritis (18.3%), reactive arthritis (19%), and enteropathic arthropathy (22.4%) were the most common clinical symptoms. The study findings among the South Indian community by Vikram Haridas et al.²¹ Suggested that 74% of people had AS. Sacroiliitis was formerly difficult to diagnose using radiological evidence, but more advanced technologies like MRI have made this process easier. In research conducted by Uma Maheshwari et al., HLA-B27 + individuals presenting with SpA had alterations detected by MRI (92% sensitivity).¹⁷ The main symptoms reported were Knee pain in 86 patients, neck pain in 38 patients, and 37 patients with lower back pain. Uveitis affected 15 individuals, and the only extra-articular symptoms identified were 19 skin rashes. In compliance with the findings of Uma Maheshwari et al.,³⁶ Joint involvement has been seen in 20% of patients; subsequently, extra-articular symptoms like persistent UTI (14%), ophthalmic as well as cutaneous involvement (8%), and CVS involvement (6%) were reported. The study findings of Vaidya B et al.³ and Menon B et al.³⁹ show (70.5%) of large joint aches and (53.9%) of inflammatory spinal pain are more common in patients with SpA.

CONCLUSION

We concluded that HLA-B27 was positive among more than half of the patient population. Detecting HLA-B27 in the early stage may aid in changing lifestyle to prevent Spondyloarthritis. HLA- B27*05 and B27*04 are the most prevalent among the patient population. IL-17 and IL-23 were both found to be significantly increased in the patient population with positive HLA-B27. Both the inflammatory markers were high in men compared to women. This information is crucial for physicians because it can help them develop an effective treatment plan. Family screening is essential to

detect HLA-B27 in its early stages and to find the familial aggregation and genetic predisposition as contributing factors to Spondyloarthritides.

ACKNOWLEDGMENTS

The authors would like to thank Miss. S. Rachel for her support in writing the manuscript, and also acknowledge the continuous assistance provided by our lab technicians, Mrs. Julies Lydia Y, Mrs. Sujatha, Mrs. Jagadammal and Ms. Durgapriya throughout the study period.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS' CONTRIBUTION

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

FUNDING

None.

DATA AVAILABILITY

All datasets generated or analyzed during this study are included in the manuscript.

ETHICS STATEMENT

This study was approved by the Institutional Ethics Committee, SRM Medical College Hospital and Research Centre, Tamil Nadu, India, with wide reference No: 1209/IEC/2017.

INFORMED CONSENT

Written informed consent was obtained from the participants before enrolling in the study.

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