Ankylosing Spondylitis: A Systematic Review of Demographics, Clinical Features, Biomarkers, and Risk Factors

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Ankylosing Spondylitis (AS) is characterized as an autoimmune response that primarily affects the neck, spine joints, and sacroiliac joints. The aim of this study is to evaluate the clinical features and provide valuable insights into the complex nature of AS. PubMed literature searches were conducted to find AS patient information. The data included information from 212,490 patients diagnosed with AS from 71 literature. The mean age of patients with AS was 55.1, 99.2% of patients had reported back pain, and 92.4% were *HLA-B27* positive, all of which are consistent with previous studies observing patients with AS. This study found that 37.8% of patients with AS had family history of spondyloarthritis, which is more reliable as this study had a larger sample size. This study also found that 20.3% of patients with AS also had arthritis. This correlation was not investigated in most previous studies observing patients with AS, and should be further investigated in future studies.

Introduction

Overview of Ankylosing Spondylitis (AS)

AS is a medical condition that falls under the spondyloarthritis group of diseases. It is characterized by an autoimmune response that primarily affects the neck, spine joints, and sacroiliac joints. Individuals with AS commonly experience stiffness and discomfort originating from the lower back and progressing upwards towards the neck. This inflammation later leads to the spine completely fusing which results in immobility of the spine and neck. The underlying cause is the fusion of ligaments and discs between the vertebrae, which is a result of the autoimmune nature of this condition [1]. Autoimmune diseases are defined by the body's immune system mistakenly identifying its own healthy cells as potentially harmful foreign entities. In AS, instead of identifying and attacking foreign cells, the immune system attacks healthy tissue surrounding joints. This is what causes the fusion in the backs and necks of AS patients [1].

Pre-existing Research

Previous patient data has shown a gender disparity among AS patients. AS is notably more common among males than females. As shown in a previous study, the number of males in the study was 8609 whereas the number of females was only 4435 [2]. AS has also shown to be most common in Caucasians. A study found that among participants, 2.25% were Asians, 8.38% were Black, 8.19% were Hispanic, 61.58% were White and the other 19.6% were not specified [3]. Evidently, the largest ethnic group within this study was Caucasian. Another factor that is of significance is age. A previous study demonstrates the distribution of AS patients in each age range as shown in Figure 1. This shows the mean age to be 49.1 with most patients being diagnosed after the age of 45 [4].

Diagnosis of Ankylosing Spondylitis (AS)

AS can be a complicated condition to diagnose because there are no standard tests to determine whether or not a patient has AS [5]. As a result, finding trends in common clinical features including back pain and arthritis can help future AS patients get an earlier diagnosis. To initially diagnose AS, doctors may assess symptoms like back pain through a physical examination, which involves testing various movements of the spine and applying pressure to specific areas to locate the source of pain. Subsequently, magnetic resonance images (MRIs) and x-rays can reveal visible indications of ankylosing spondylitis such as arthritis. While there are no specific tests to identify AS, imaging and physical examinations can provide information regarding certain clinical features involved with AS [6]. Once such clinical features have been identified, patients can get an AS diagnosis.

Prognosis of Ankylosing Spondylitis (AS)

In addition to looking at clinical features, doctors may look at risk factors such as family history. It has been shown that AS is more likely to occur in patients who have a first degree relative already affected by AS [7]. Similarly, doctors may look at the *HLA-B27* gene as there has recently been found to be a correlation between *HLA-B27* positivity and AS diagnosis.

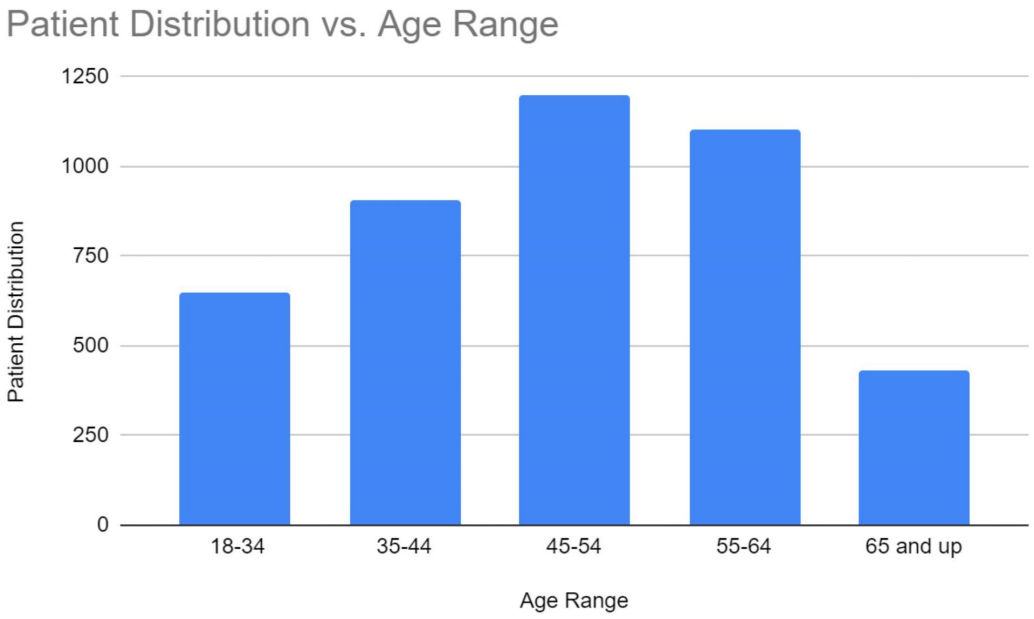

Fig. 1 The age distribution of diagnosis of AS[4], mean age: 49.1

HLA-B27 (Human Leukocyte Antigen B27) is a protein found on the surface of white blood cells. It helps the body differentiate between its own cells and foreign cells. To test for *HLA-B27*, doctors run a blood test and determine whether or not a patient is *HLA-B27* positive. If a patient is positive, they are at a higher risk for certain autoimmune diseases including AS[8]. By looking at such risk factors associated with this condition, doctors may be able to efficiently predict the development of AS within a patient or family.

Biomarker of Ankylosing Spondylitis (AS)

The most prominent biomarker for AS is the presence of *HLA-B27*. Blood tests can help determine if the patient carries *HLA-B27*, which is present in 80-90% of AS patients. However, being *HLA-B27* positive does not guarantee the presence of AS[9]. Looking at this biomarker combined with clinical features can contribute to a more accurate diagnosis of AS. In addition to *HLA-B27*, ERAP-1 and MMP-3 are biomarkers that have recently been linked to AS. Prior research on ERAP-1 observes that ERAP-1 is only associated with AS in patients that are *HLA-B27* positive as well. Research indicates that within AS patients, single nucleotide polymorphisms (SNP) are present in the ERAP-1 gene. Specifically, there seems to be a correlation between ERAP-1 rs27044 SNP in AS patients of Asian and European populations. Studies have also suggested a correlation between a protein called serum MMP-3 and AS in patients with joint swelling. The level of serum MMP-3 seems to relate to the severity of inflammation in patients with forms of arthritis. MMP-3 levels have been found to correspond with disease activity in spinal and peripheral symptoms of AS[10]. Studying this correlation can be useful for AS diagnosis and treatment.

Aim of Study

Our research focuses on the patient data of those who have been diagnosed with AS. The information covered includes demographics, clinical features, biomarkers, and risk factors associated with AS. Demographics include data about patients' age, gender, ethnicity, and race. Risk factors include family history. Clinical features include patients' symptoms such as arthritis and back pain. Biomarkers include the presence of *HLA-B27* in AS patients. This study aims to evaluate the clinical traits that may assist in the diagnosis of AS in future patients. Prior research on this condition fails to provide a concise, comprehensive analysis of multiple features of AS. For example, it should be noted that while past reviews have included a lot of information about *HLA-B27*, they have put less emphasis on the correlation between arthritis and AS, and the significance of arthritis as a clinical feature for this condition. This review aims to provide a more inclusive analysis of the different factors that may contribute to the development of AS in patients.

Results

Demographics

The study included information from 212,490 patients diagnosed with AS from 71 literatures. 66,377 were males, 23,503 were females, and 122,611 patients with unknown gender information. Our findings reflect AS to be more prominent in males than females: 73.9% versus 26.1% respectively . The mean age of diagnosis is 55.1 years old, with ages ranging between 18 and 91. As for correlation with race/ethnicity, as shown in Figure 2, there are 94,952 (87.2%) White patients, 7,332 (6.7%) Black patients, 3,466 (3.2%) Hispanic patients, 3,107 (2.9%) Asian/Pacific Islander patients, and 84 (0.077%) Native American/Alaskan Native patients (too small to see in Figure 2).

Biomarkers

To study the biomarkers, we examined the prevalence of the *HLA-B27* positivity in the AS participants . We found that 10,651 patients had available *HLA-B27* tests of which 9,845 patient tests reported them to be *HLA-B27* positive. This resulted in a 92.4% prevalence of *HLA-B27* in our data set.

Risk Factors

The risk factor investigated in the present study includes family history for conditions in the spondyloarthritis group. Of the 983 patients who had family history data available, 372 reported having family members who were already diagnosed with some form of spondyloarthritis, indicating a 37.8% occurrence of family history being a risk factor in this data set.

Clinical Features

As shown in Figure 3, 5,041 patients had available data regarding back pain of which 5,000 patients were reported to suffer with back pain. This resulted in a 99.2% occurrence of back pain in our data set. As for arthritis, 2,299 patients had available data regarding arthritis of which 467 were reported to have arthritis. This resulted in a 20.3% occurrence of arthritis in this data set.

Discussion

Demographics

The demographic characteristics of AS patients vary across different populations. This study only includes information from adult patients. This is consistent with previous studies that have identified AS as typically being diagnosed in adulthood for most patients. This can also be the result of recruitment bias as other studies mainly focus on adult patients with AS. Also consistent with previous studies, our data set shows a much higher number of male patients than female patients. This can be due to less patient data available for women than there is for men. As for race and ethnicity of AS epidemiology, AS is present in diverse racial and ethnic groups, but our research shows its high prevalence in the white population. (Figure 2), which represents 87.2%. Nevertheless, this can be attributed to recruitment bias.

Clinical Features

Back pain is a significant feature of AS. Our review showed that back pain is a primary symptom. Previous studies show 92.7-100% of AS patients also have back pain, which is consistent with the findings in this study[11,12]. Nevertheless, since patients may only be referred for diagnosis of AS only when back pain is present, this can be a recruitment bias for diagnosis of AS. This may also explain why this study found such a high occurrence of back pain in AS patients. Arthritis is another key clinical feature of AS. While most previous studies did not investigate the association between arthritis and AS, our analysis highlights the frequency of arthritis in AS patients. Because arthritis is also a condition that affects bones and joints, the association between arthritis and AS can be significant in AS diagnosis and can lead to answering more questions about the cause of AS. It can also be a useful tool in the diagnosis of AS as the correlation between arthritis and AS is studied more in the future.

Biomarkers

Around 8% of the general population is *HLA-B27* positive and around 80-90% of AS patients are *HLA-B27* positive[9]. Consistent with these numbers, our data set had over a 90% prevalence of *HLA-B27*. The association between *HLA-B27* positivity and the development of AS is notable across a number of studies and can be extremely beneficial in AS diagnosis as well. *HLA-B27* also contributes to the heritability of AS, which makes it more likely to be passed onto future generations. This aspect of *HLA-B27* also relates to the genetic aspect of this disease and may help establish a correlation between AS and genetics in the future.

Risk Factors

Risk factors, such as family history, can contribute to the development of AS. Previous studies show 11.9-62.2% occurrence of family history within AS patients[13,14]. These studies provided a large range of occurrences for this risk factor. The present study has a larger sample size and hence provides

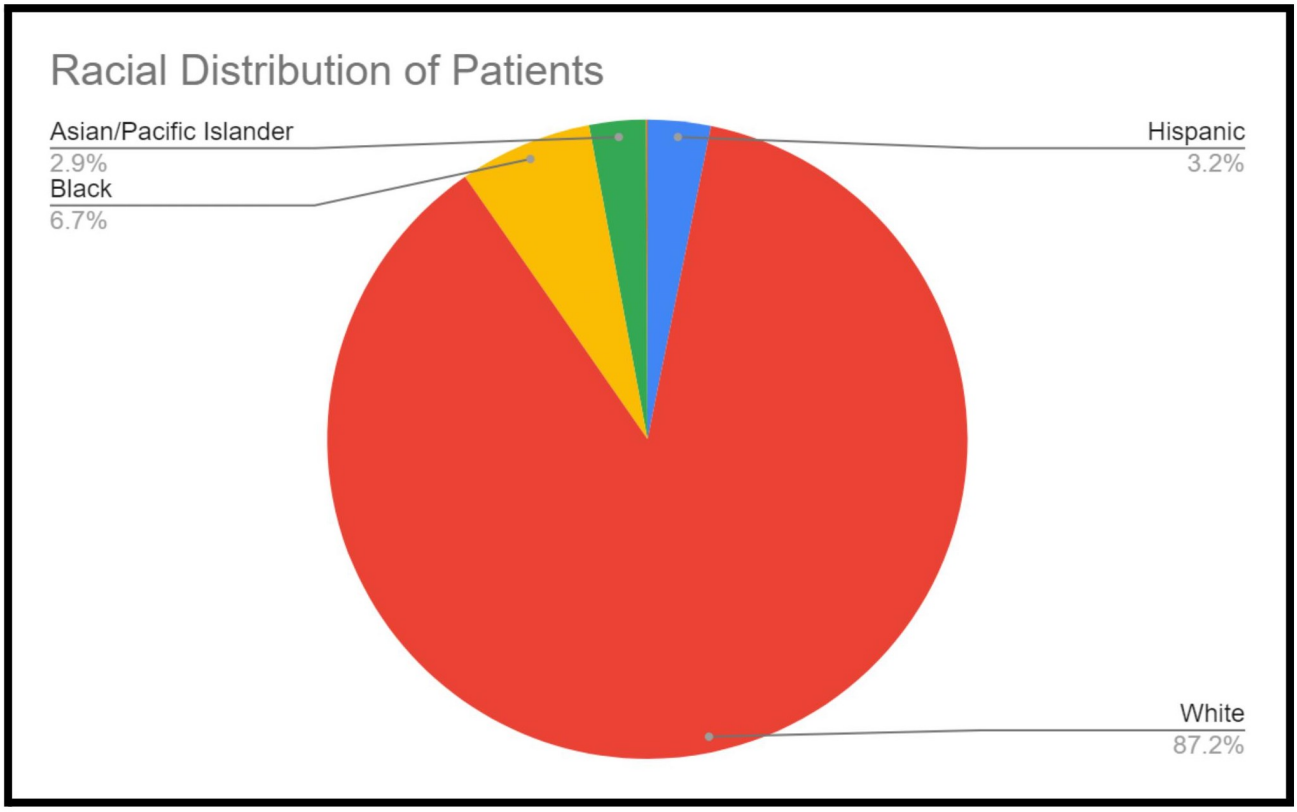

Fig. 2 The ethical distribution of patients with AS not including patients whose race data was unavailable. 94,952/212,490 (87.2%) patients were White, 7,332/212,490 (6.7%) patients were Black, 3,466/212,490 (3.2%) patients were Hispanic, 3,107/212,490 (2.9%) patients were Asian/Pacific Islander, and 84/212,490 (0.077%) patients were Native American/Alaskan Native

more reliable data about family history. As this study aims to provide a more comprehensive analysis of the factors affecting AS development, the narrower results show a more reliable occurrence of family history in AS patients than previous studies. As more data is collected regarding family history and the role it plays in AS development, this risk factor can also be used as a tool for early AS diagnosis and treatment.

Limitations

A limitation of our research was the lack of individual patient data available. Many studies had information regarding the condition, but didn't have information about each patient. We specifically lacked access to detailed age distribution from studies. This restricted our access to data that could be analyzed for our research. Furthermore, many data sets had recruitment biases in gender, race, and age. Most literature studied in this systematic review only had data on males over females. All literature studied in this systematic review had more white patients than other racial/ethnic groups and only had data for adults. This made it difficult to have a fully representative data set in our own study. Therefore, future studies can be improved by including complete gender data from both males and females, have similar distribution of different racial/ethnic groups, and should also include data from younger (below 18) age groups. Additionally, this review only includes literature from the PubMed database, written in English, and including patient data from the United States as these were the most accessible in this study. Because of this, another limitation of this study is that it is only representative of the U.S. AS patient population rather than the population of AS patients globally. Patient data was also only used if it was provided for individual patients rather than a population of patients. This ensured that all data was more precise and accurate, but also reduced the number of literature that were included.

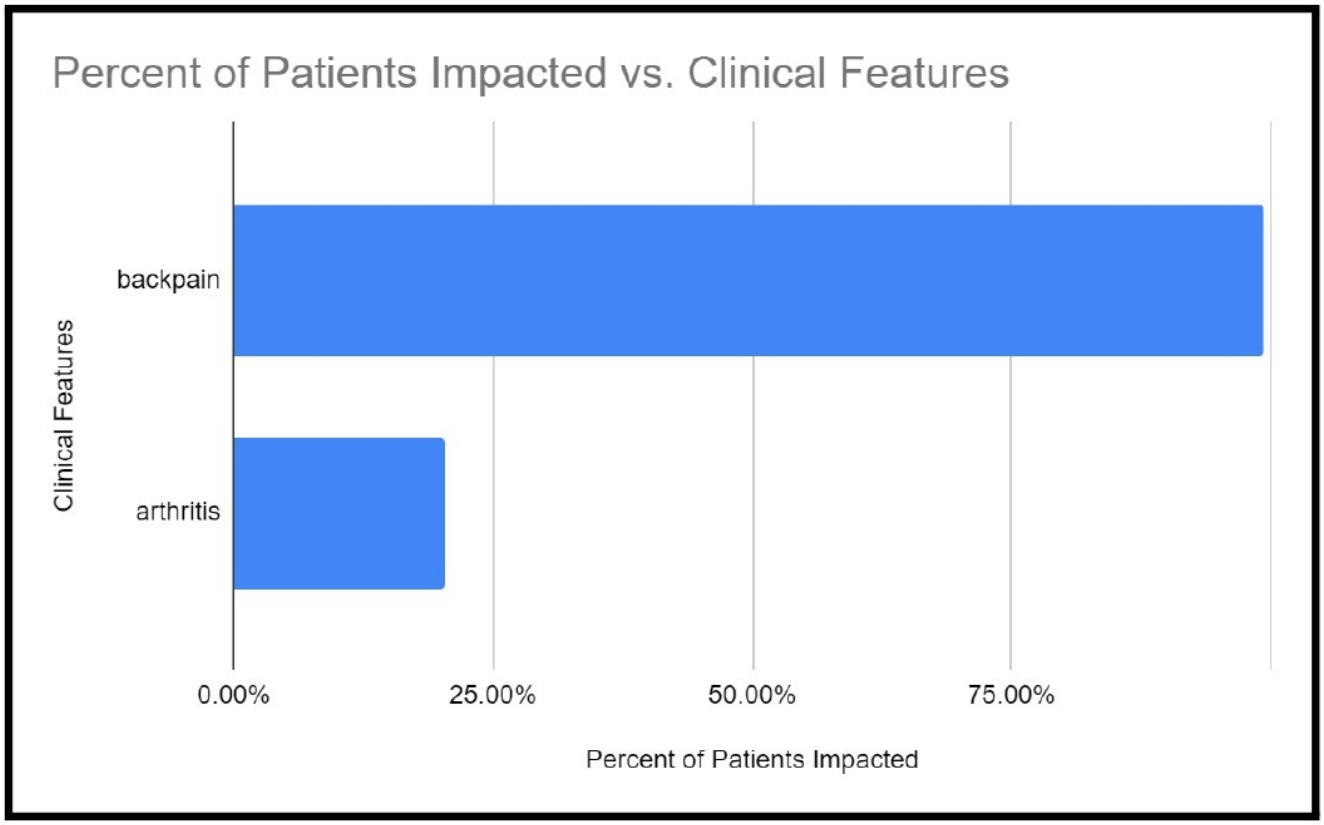

Fig. 3 The distribution of patients with symptoms not including the patients whose data for these clinical features was unavailable. 5,000/5,041 (99.20%) patients reported back pain and 2,299/5,041 (20.3%) patients were diagnosed with arthritis.

Methods

PubMed literature searches were conducted using the key word search [”ankylosing spondylitis” AND (”*HLA-B27*” OR ”back pain” OR ”arthritis”) AND ”US”]. The search was executed on August 6, 2023. The initial search yielded 294 matches. Of which, 45 articles were inaccessible and consequently excluded. An additional 164 articles were omitted due to their deficiency in relevant AS patient data. Furthermore, 14 articles were disregarded for not being authored in English. The remaining 71 literatures were used as shown in the PRISMA flowchart in Figure 4. PRISMA guidelines were followed when determining which literatures would be included in this study, collecting the data, and analyzing the data. Patient data collected from these literatures included patient age, gender, race/ethnicity, occurrence of back pain, presence of arthritis, presence of *HLA-B27*, and occurrence of family history. Using this data an analysis was conducted to determine the mean age, range of ages, ethnic distribution, presence of back pain, arthritis, and presence of *HLA-B27* (See appendix for AS Systematic Review Final Supplementary).

Conclusion

In conclusion, this systematic review provides a comprehensive synthesis of AS demographics, clinical features, biomarkers, and risk factors. By analyzing the patient data collected from other literatures, we found traits that may support patterns in the general AS population. We found the mean and range ages of our data set, the gender distribution, racial/ethnic distribution, occurrence of back pain and arthritis, presence of *HLA-B27*, and existence of family history within our data set. A key finding of this study is that 20.3% of patients in this data set had arthritis, which was seldom reported in previous studies. An increase in data to support the association between AS and arthritis may serve as a helpful diagnosis tool in the future. Because of this, it would be beneficial for future studies to emphasize the study of the relationship between arthritis and AS. It was also found that a higher percentage (92.4%) of patients with AS in this study were *HLA-B27* positive com-

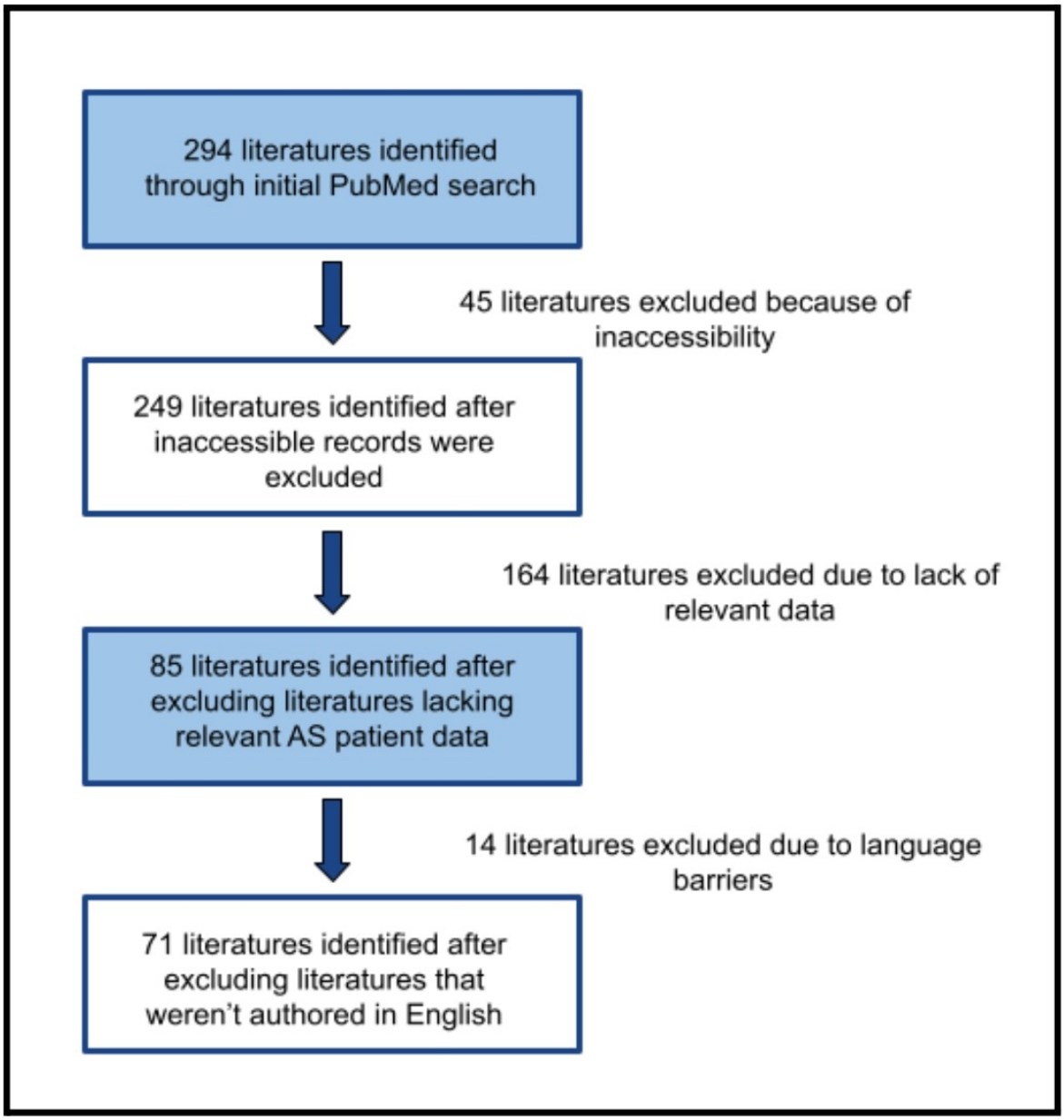

Fig. 4 PRISMA Flowchart with literature exclusion process.

pared to previous studies. This strong association is consistent with the findings of past studies as well and may serve as an important indicator of AS. Another key finding was a 37.8% occurrence of family history within AS patients. This is more reliable data than previous studies as it offers a narrower, more precise percentage rather than a range of occurrence of family history. It would also be beneficial for future studies to focus on this risk factor as past studies had limited data about it and it can be a key indicator of AS.

Acknowledgements

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Ankylosing Spondylitis: A Systematic Review of Demographics, Clinical Features, Biomarkers, and Risk Factors Supplementary Table:

PMID	# of patients	Female	Male	Age	Ethnicity/Race	Back Pain	Arthritis	HLA-B27	Family history
26987341	3336	NA	NA	range: 18-64 mean: 44.7	NA	3336	NA	NA	NA
25917849	7772	NA	NA	NA	NA	NA	NA	7772 (they only looked at HLA-B27 positive patients in the study)	
30210584	356	NA	NA	NA	NA	all patients with back pain Visual Analog Scale (VAS) score of ⩾4	NA	NA	NA
27445458	620	NA	NA	NA	NA	NA	NA	NA	NA
29409123	310	NA	200	mean +/- SD (49.2 ± 14.3), 18 and older	white=279, asian=6, black=5, pacific islander=1, mixed race=4, other=3	310	NA	Patients with available HLA–B27 test results (reported on laboratory form):154 Positive test result (among patients with available test results): 102 HLA–B27 positivity (physician reported):200	37
26628601	4288	1530	2758	mean: 49.1 (SD:13.4), 18-34: 649, 35-44: 906, 45-54: 1199, 55-64: 1101, 65 and up: 433	NA	NA	NA	NA	NA

35672618	646	272	374	mean: 42.88, SD: 13.2, 18–39:273, 40–64:344 ,65–74 :19, ≥75: 10	NA	NA	NA	NA	NA
18383414	591	NA	NA	18-87 mean age: 48.9	NA	NA	NA	NA	NA
34564835	17794	8649	NA	mean: 57.2	asians: 401 black: 1492 white: 10957 hispanic: 1457 not specified: 3487	NA	NA	NA	NA
18357499	216	NA	NA	age: 18-70, mean: 38.1 ± 10.6	NA	NA	Peripheral arthritis was present in 29.4% of patients. Hip joint: 9.3% knee joint: 8.5% shoulder joint: 6.1%	HLA-B27 was investigated in 31.1.% of patients. Rate of positivity was 91%	NA
28652703	86	NA	NA	NA	NA	NA	NA	NA	NA
27790010	315	NA	NA	NA	NA	total back pain score ≥4 cm (on a 0–10 cm visual analog scale [VAS]	NA	NA	NA
35768880	10940	5760	5180		white: 8900 black: 940 other: 1100	NA	NA	NA	NA
30260423	79	29	50	Mean: 44.4 (SD 11)	NA	NA	NA	44/65 (67.7%)	NA
29666980	29	NA	NA	NA	NA	NA	NA	NA	NA
32442295	13,044	4435	8609	65 (all data came from medicare enrollment)	white:11,858 black:514 other:672	NA	NA	NA	NA

34459565	438	72	366	≤24: 61 25–34 :164 35–44 :144 ≥45: 69 Mean ± SD (median)‡ 34.69 ± 8.63 (34)	White :307 Black :84 Asian or Pacific Islander: 24 Other, mixed or unknown:23	406 patients with lower back pain	NA	NA	NA
33452168	2057	946	NA	Mean: 58.2	NA	NA	417 (rheumatoid arthritis)	NA	NA
36333490	581	238	NA	Mean:50.2	Caucasian: 411	NA	NA	NA	NA
33607385	639	179	460	50 ± 12	NA	NA	NA	460 positive	NA
26337538	1519	48	NA	18-34: 180, 35-44: 257, 45-54: 354, 55-63: 514, >63: 214	NA	NA	NA	NA	NA
33858974	414	156	252	NA	NA	NA	NA	NA	NA
31663467	935	NA	886	mean: 57.6	ETHNICITY - hispanic: 38 non-hispanic: 866 unknown: 31 RACE - white: 732 black: 103 other: 59 unknown: 41	NA	NA	NA	NA
31371654	119	NA	82	mean: 50.85 ± 14.77	white: 96 other: 23	NA	NA	NA	NA
30868287	2254	NA	NA	NA	NA	NA	NA	NA	NA
35481333	50	17	33	62-73, median: 68	NA	NA	NA	NA	NA
29961693	52,568	NA	NA	mean: 59.3 ± 11.4 years	NA	NA	NA	NA	NA

36001102	334	206	128	mean: 54.4, SD: 14.3	white: 282	n=285, mild: 72, moderate/severe: 203	NA	NA	NA
8777859	1	0	1	35	NA	1	NA	NA	NA
30371264	42,327	NA	26,796	Age 65–69 y: 11 477 Age 70–74 y: 9097 Age 75–79 y: 8631 Age 80 y or older: 13 122	White: 38,167 Black: 1863 Hispanic: 542 Asian: 776 Other: 979	NA	NA	NA	NA
29589132	1178	NA	834	mean: 36.57, SD:12.78	all chinese	NA	NA	752 positive	NA
29196383	706	NA	NA	NA	NA	NA	NA	NA	NA
31041666	235	174	61	mean: 49.8	white: 218 black/african american: 5 american indian/alaska native: 5 asian: 0 unknown: 2	NA	NA	NA	NA
30094388	1690	326	946	NA	ETHNICITY-hispanic/latino: 94, not:1178 RACE-white:1033, black: 49, asian: 86, Native American Indian or Alaskan Native (Hispanic): 75, Native Hawaiian or Other Pacific Islander: 0, mixed race: 28, unknown: 1	NA	NA	NA	NA
31985181	24	NA	NA	37.5 ± 5.6	NA	NA	NA	NA	NA

30353387	155	NA	114	mean: 47.9	white: 140, asian: 3, black: 2, pacific islander: 0, mixed race: 3, other: 1	NA	NA	Patients with available HLA-B27 test result: 108, Positive test result (among patients with available test results): 80	Family history of SpA: 23
29142040	1150	NA	NA	NA	NA	NA	NA	NA	NA
29669197	2773	NA	NA	younger than 75, 61.1 ± 10.8	NA	NA	NA	NA	NA
33568191	80	NA	NA	NA	NA	NA	NA	NA	NA
16082640	169	NA	NA	mean: 38-43	NA	NA	NA	NA	NA
28109577	28	8	20	51 ± 12.31	NA	NA	NA	NA	NA
18512723	397	NA	NA	NA	NA	NA	NA	NA	NA
26990731	1011	NA	NA	NA	NA	NA	NA	NA	NA
30088115	14,714	NA	8804	41.8 ± 11.9	white: 9471, black: 1722, hispanic: 1377, asian: 572, other: 1572	NA	NA	NA	NA
23334425	36	16	NA	35.2 ± 8.9	NA	NA	NA	NA	NA
22836244	1	0	1	32	white	NA	NA	1	NA
12228161	27	NA	NA	NA	NA	NA	NA	NA	NA
31221884	7686	NA	NA	mean:44.6	NA	16%	NA	NA	NA
36470752	12,451	NA	8193	65 and up	white: 11282, black: 501, other: 668	NA	NA	NA	NA
28891005	35	0	35	35.17 ± 8.05	NA	NA	NA	NA	NA
23604547	1	0	1	42	NA	yes	NA	positive	no
32999362	13	2	11	mean: 50 range: 47-67	NA	NA	NA	9/13 (69.2%)	NA
22257916	493	NA	NA	NA	NA	NA	NA	NA	NA
22231927	502	NA	NA	NA	NA	NA	NA	NA	312

Fig. 9

19369461	100	NA	NA	mean: 61 ± 13	NA	NA	NA	NA	NA
36153800	409	196	213	mean: 54.5 ± 16.2 median: 55 range: 19-89 age groups: 0-17: 0 (0%) 18-44: 116 (28.4%) 45-64: 169 (41.3%) 65-74: 76 (18.6%) 75-84: 38 (9.3%) 85+: 10 (2.4%)	RACE-Caucasian: 328 (80.2%) African American: 40 (9.8%) Asian: 9 (2.2%) Other/Unknown: 32 (7.8%) ETHNICITY-Hispanic: 31 (7.6%) Not Hispanic: 355 (86.8%) Unknown: 23 (5.6%)	NA	NA	NA	NA
21360492	158	NA	NA	older than 18	NA	NA	NA	NA	NA
29222625	22	NA	NA	NA	NA	NA	NA	NA	NA
31056582	1	0	1	36	NA	NA	NA	positive	NA
30157925	125	47	78	Age at time of study (years), mean ± SD : 48.3 ± 9.6 Age at time of diagnosis (years), mean ± SD : 39.5 ± 9.6	NA	NA	NA	92 (74.8%)	NA
12509614	44	0	44	mean:44+/-12	Japanese	NA	NA	NA	NA
11727838	51	12	39	mean:46.8	NA	NA	NA	45 positive	NA
17938137	15	0	15	range:51-91	NA	NA	NA	0	0

16208654	326	NA	241	55.0 ± 10.7	white: 284 (87.1%) african-american: 12 (3.7%) asian/pacific islander: 7 (2.1%) native american: 4 (1.2%) hispanic: 17 (5.2%) other: 2 (0.6%)	NA	NA	NA	NA
9382668	23	8	15	NA	NA	NA	NA	NA	NA
11817595	241	NA	167	47.1 +/- 13.8	206 white	NA	49 peripheral arthritis	NA	NA
32124128	527	176	351	39.9 ± 12.7	NA	NA	NA	485 positive	NA
28966206	18	NA	16	mean: 44	NA	NA	NA	NA	NA
28742241	1	0	1	50	NA	NA	osteoarthritis in the lower lumbar spine	NA	NA
16169767	215	NA	NA	NA	NA	NA	NA	NA	NA
8635287	1	0	1	NA	NA	NA	NA	positive	NA