Research hotspots and trends analysis of ankylosing spondylitis: a bibliometric and scientometric analysis from 2009 to 2018

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Background: This study utilized bibliometric analysis to qualitatively and quantitatively analyze hotspots and predict trends in the field of ankylosing spondylitis (AS) research.

Methods: Articles about AS were obtained from the Web of Science Core Collection and PubMed database, and bibliometric analysis was carried out through CiteSpace and the Online Analysis Platform of Literature Metrology and Bibliographic Item Co-Occurrence Matrix Builder (BICOMB). Then, co-word biclustering analysis was conducted to obtain research hotspots and predict trends using gCLUTO software.

Results: A total of 6,818 articles on AS from 2009 to 2018 were analyzed, showing an increasing publication trend (558 articles in 2009 to 851 articles in 2018). The *Journal of Rheumatology* was the leading journal in AS research, with an impact factor (IF) of 3.634 and H-index value of 49. In terms of region, the United States led the world in this field, and The University of Toronto was the leading institution for AS research. Van Der Heijde, D was the most prolific author in the field. Eight research hotspots in the field of AS were also identified.

Conclusions: Our analysis identified eight research hotspots, and predicted that surgical treatment and etiology will be the main AS research trends in the future. This study provides new directions and ideas for future research in AS.

Keywords: Ankylosing spondylitis (AS); bibliometric analysis; co-word analysis; biclustering; hotspots

Introduction

Ankylosing spondylitis (AS) is an immune-mediated chronic disease, and one of the most common arthropathic diseases. It mainly affects the axial skeleton, causing spinal structural damage, which can lead to back pain, stiffness, and limited lumbar movement. Disease onset typically occurs after the age of 30, and the disease mainly affects males, with an incidence approximately 2–3 times that of women (1,2). In recent years, however, due to AS attracting more attention and diagnostic improvements, a larger number of children aged 6–10 years are also being diagnosed. Due to

this younger age of onset, understanding AS is particularly important and urgent. While the pathophysiology of AS is not yet fully understood, studies on twins have shown that the disease is more than 90% hereditary (3). HLA-B27 expression is also closely correlated with AS, but its role in AS onset is not yet clear.

The main treatment approach in AS is medication, including anti-TNF agents and non-steroidal anti-inflammatory drugs (NSAIDS). The interleukin-17 inhibitor secukinumab also has demonstrated efficacy in the management of AS (4). However, the efficacy, correct dosage, and safety of various drugs have yet to be fully

Page 2 of 15

Liang et al. Research hotspots analysis of AS

investigated. In recent years, surgical treatment has also garnered more attention, but the choice of specific surgical methods and treatment efficacy remain controversial. Currently, no standard treatment for AS exists, and the current research trends in the field are not well defined. Hence, summarizing research trends is important for future researchers' understanding of AS, and in helping to identify where to focus research efforts to best help AS patients. Therefore, this study investigated research hotspots to help future researchers fill in the knowledge gaps in the field of AS.

Bibliometrics is a widely used methodology which uses statistical methods to analyze the quality of research, and to reveal research hotspots and research trends in a specific topic area. It also utilizes statistical indexes to evaluate the contribution of scientific publications in a particular research area. Bibliometrics uses statistical analysis including cluster analysis and factor analysis to define research hotspots and the structure of the subject, then classify the keywords of the topic. Cluster analysis is the most commonly used method. Different from traditional clustering, biclustering not only processes the global information but also allows the rows and columns of the matrix to be processed simultaneously so that it can detect local messages more efficiently when encountering high-dimensional data. Biclustering analysis has been widely utilized in recent years in the area of bibliometrics. Through biclustering, Yan *et al.* discovered the cytokine clusters associated with the prognosis of chronic lymphocytic leukemia (5). The miRNA expression profiles of breast cancer were also revealed by researchers using biclustering (6). We also previously predicted the research hotspots in postmenopausal osteoporosis through the biclustering method (7). These previous studies demonstrate that the biclustering analysis method can effectively reveal the hotspots of research and provide direction for future AS research.

Currently, few bibliometric studies on AS exist. In this study, we analyzed relevant publications between 2009 and 2018 to ascertain the current research situation and progress in AS. Furthermore, we adopted a co-word biclustering analysis method to clarify research hotspots in AS. It is hoped that this study will provide new directions and ideas for future research in AS.

Methods

Data source and search strategy

Literature about AS was extracted from the Social Science

Citation Index and the Science Citation Index-Expanded from the Web of Science Core Collection (WoSCC) on December 2, 2019. The search terms "Spondylitis, Ankylosing AND Language = English", were used, with a time limitation between January 1st, 2009 and December 31st, 2018. Original articles and reviews in English were the only publication types collected. PubMed was also used, as MeSH (Medical Subject Headings) terms were able to represent the subject of the articles and enabled us to carry out continuous co-word clustering analysis (8). Additionally, to prevent inaccuracies caused by data updates, all data were collected on the same day.

Data collection

Two researchers independently screened the search results with a consensus rating of 0.9. Any differences were discussed to reach an agreement. Data in text format were converted from the WoSCC data and imported into CiteSpace 5.7.R1, 64bit (Drexel University, Philadelphia, PA, USA) and the Online Analysis Platform of Literature Metrology (http://bibliometric.com/) for bibliometric analysis. Each article downloaded from PubMed was imported in XML format into Bibliographic Item Co-Occurrence Matrix Builder (BICOMB) for the following hotspot analyses (9).
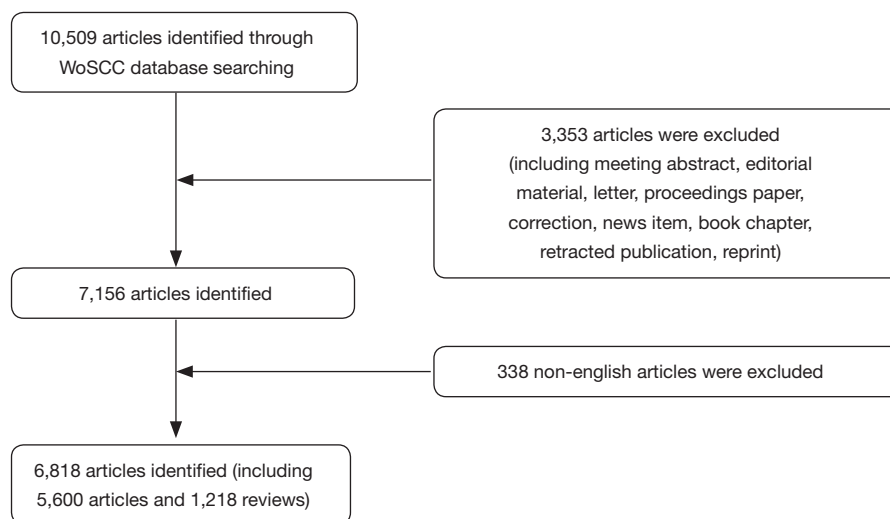
Data analysis

Bibliometric analysis

The characteristics of the retrieved articles were summarized, including author details, institution, journal, country, citations, H index, and annual publications. We also evaluated the impact factors (IF) and citations obtained from *Journal Citation Reports* (*JCR*) 2018, and then collected the characteristics of the publication's reputation and influence. The annual publication numbers and growth trends were analyzed using the Literature Metrology online analysis platform. CiteSpace was used to connect authors, institutions, journals, countries, and other factors into a network for analysis. CiteSpace also facilitated the extraction of a certain number of papers within a specified number of years into a single network through the "time-slicing" function. We chose different node types, and the number of publications and citations were represented by their sizes (10,11).

Co-word biclustering analysis

Major MeSH terms/MeSH subheading terms were

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┌─────────────────────────────┐
│ 10,509 articles identified  │
│ through WoSCC database      │
│ searching                   │
└─────────────────────────────┘
              │
              │         ┌──────────────────────────────────┐
              │         │ 3,353 articles were excluded     │
              ├────────▶│ (including meeting abstract,      │
              │         │ editorial material, letter,       │
              │         │ proceedings paper, correction,    │
              │         │ news item, book chapter,          │
              │         │ retracted publication, reprint)   │
              │         └──────────────────────────────────┘
              ▼
┌─────────────────────────────┐
│ 7,156 articles identified   │
└─────────────────────────────┘
              │         ┌──────────────────────────────────┐
              ├────────▶│ 338 non-english articles were    │
              │         │ excluded                          │
              │         └──────────────────────────────────┘
              ▼
┌─────────────────────────────┐
│ 6,818 articles identified   │
│ (including 5,600 articles    │
│ and 1,218 reviews)          │
└─────────────────────────────┘
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Figure 1 Flow chart of literature filtering performed in this study.

analyzed with BICOMB and Microsoft Excel, and their frequency permutations in proportion to the related literature were determined. The MeSH terms that occurred at high frequencies were analyzed, and the trends were determined. A biclustering analysis of these terms was also carried out, and publications were selected to determine the research hotspots of AS. Biclustering was used to reveal the relationship between source articles and high-frequency terms, and the relationship between high-frequency terms. We used the high-frequency terms as rows and the source articles as columns. gCLUTO 1.0 (Graphical CLUstering Toolkit) software developed by Rasmussen *et al.* was used to construct a binary matrix for biclustering analysis (12). Parameters suitable for biclustering analysis in gCLUTO were set according to the literature. I^2 was determined as a standard function, and Cosine as a similarity function. The clustering method was repeated in bisects. The results of the biclustering analyses were presented in the form of a mountain visualization and matrix visualization. We redirected biclustering with various cluster numbers until the optimal matrix visualization and mountain visualization results were obtained. We then also mapped and established the basic structure of our research based on the semantic relationship between the terms and the typical source articles.

Ethical approval is not required because the research didn't involve human experiments.

Results

Distribution characteristics of literature

Obtaining relevant literature

According to our search strategy, our study generated a total of 6,818 English publications from 2009 to 2018, including 5,600 articles and 1,218 reviews. The literature screening strategy is shown in *Figure 1*. *Figure 2* shows the number and trends of AS-related publications over the past 10 years. The overall literature was found to be increasing, from 558 in 2009 to 851 in 2018.

Distribution characteristics of countries/regions and institutions

According to the preliminary statistics, articles about AS by active authors came from at least 89 countries, and the top 10 countries that contributed articles are listed in *Figure 3*. In the decade between 2009 and 2018, the United States [1,249] was the largest contributor to AS research, followed by China [1,091], the United Kingdom [666], Germany [608], and the Netherlands [605]. The most significant influence on other countries was Spain, with a centrality of 0.11, followed by France and Canada (both centrality =0.08) (*Table 1*). The top 10 institutions for AS research output included the University of Toronto [322], Leiden University [283], Charite [226], University of Alberta

Page 4 of 15

Liang et al. Research hotspots analysis of AS
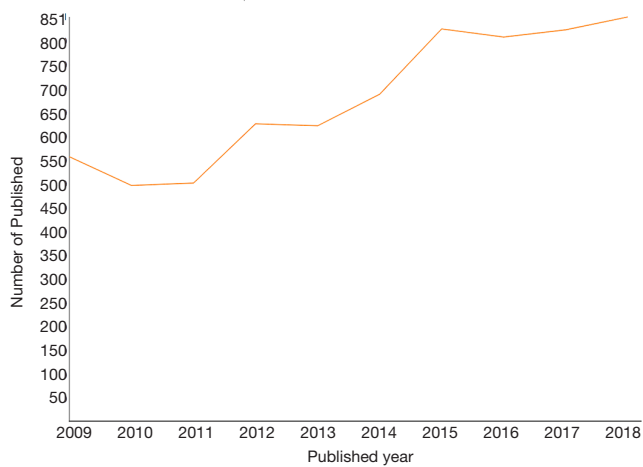
Figure 2 Output of related literature. The number of annual publications in the field of AS from 2009 to 2018.
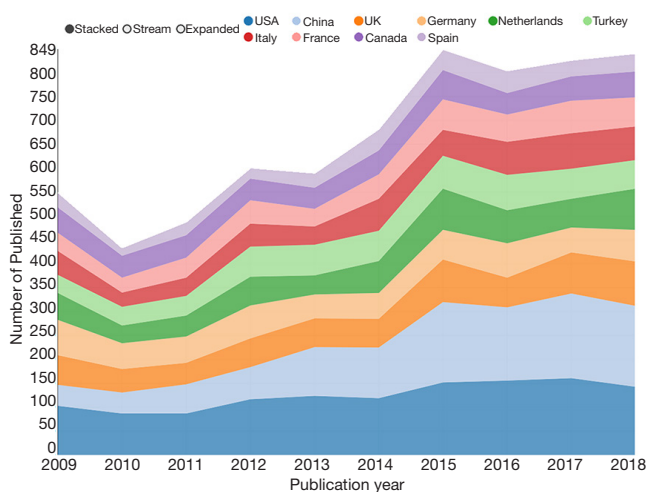
Figure 3 Output of related literature. The growth trends of the top 10 countries/regions in AS research from 2009 to 2018.

[194], and Oregon Health & Science University [176] (*Figure 3*). *Figure 4* shows the AS research network, with a density of 0.0609, which is a low-density map, indicating that the research groups are relatively scattered and the institutions do not closely collaborate. Among the top 10 institutions for AS scientific research output (*Table 1*), almost all of the central indexes were lower than 0.15 (except the University of Alberta), suggesting that most institutions have low influence and less inter-agency cooperation. *Figure 5* shows the international cooperative relationships. The United States and Canada cooperated most frequently,

followed closely by the United States and Germany.

Journal distribution

There was a total of 1,076 journals in the AS field. Of the 6,818 publications retrieved, the output of the top 10 most active AS-related journals accounted for 35.12% of them, with a total of 2,395. *Table 2* ranks the top 10 most active journals. *The Journal of Rheumatology*, *Clinical Rheumatology*, and *Annals of The Rheumatic Diseases* ranked as the top three. These three journals accounted for 15.20% of all retrieved articles in the field. The journal with the highest IF was *Annals of The Rheumatic Diseases*, with IF 14.299, followed by RHEUMATOLOGY (5.149), *Arthritis Care & Research* (4.53), *Arthritis Research & Therapy* (4.148), and *Journal of Rheumatology* (3.634). According to the *JCR* 2018 standard, these 10 most active journals were spread across Q1, Q2, and Q3 partitions.
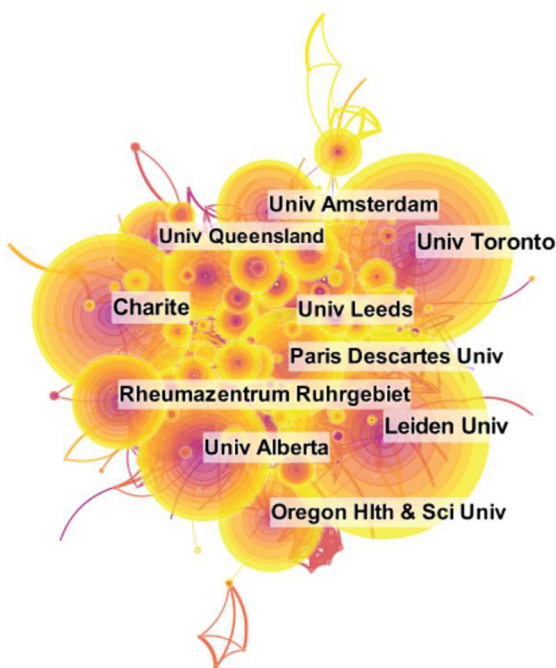
Author distribution

A total of 21,639 authors were involved in the AS studies retrieved. The top 10 authors were listed in order of the number of outputs. The most prolific researchers were: van der Heijde D, Sieper J, Braun J, Dougados M, Maksymowych WP, Inman RD, Landewe R, Baraliakos X, Brown MA, and Rudwaleit M (*Table 3*). Among them, van der Heijde D, from the Leiden University Medical Center, The Netherlands, ranked first with 208 articles, followed by Sieper from the Department of Gastroenterology, Infectious Diseases and Rheumatology, Campus Benjamin Franklin, Charité-Universitätsmedizin Berlin, Germany, with 182 articles. These two researchers have made significant contributions and have strong influence and authority in the field of AS research. CiteSpace was used to analyze the information of authors and co-cited authors, and to plot a visual network (*Figures 6,7*). The highest co-cited author is Braun J, with 2,119 co-citations, followed by Vanderlinden S [1,918], Rudwaleit M [1,522], and Van Der Heijde D [1,489]. The centrality indexes of Braun J, Rudwaleit M, Van Der Heijde D, Calin A were all greater than 0.1, indicating that they had a significant influence in the field of AS research.

Research hotspots in AS

A total of 4,493 major MeSH terms/MeSH subheading terms were obtained from the literature. The cumulative calculation frequency was 18,459. We defined terms that occurred more than 48 times after the evaluation of the H

Table 1 The top 10 countries/regions and institutions contributing to publications in ankylosing spondylitis (AS) research

Rank	Country/region	Article counts	Centrality	Institutions	Article counts	Centrality	Total number of citations	Average number of citations	Total number of first authors	Total number of first author citations	Average number of first author citations
1	USA	1249	0.05	Univ Toronto	322	0.07	4,364	13.55	62	570	9.19
2	China	1091	0.00	Leiden Univ	283	0.13	7,502	26.51	84	1479	17.61
3	UK	666	0.05	Charite	226	0.03	7,548	33.4	92	3960	43.04
4	Germany	608	0.03	Univ Alberta	194	0.16	6,514	33.58	60	1046	17.43
5	The Netherlands	605	0.01	Oregon Hlth & Sci Univ	176	0.03	2,354	13.38	53	410	7.74
6	Turkey	580	0.00	Univ Tehran Med Sci	162	0.00	723	4.46	50	197	3.94
7	Italy	538	0.04	Maastricht Univ	159	0.02	3,762	23.66	49	621	12.67
8	France	498	0.08	Paris Descartes Univ	154	0.03	2,072	13.45	45	478	10.62
9	Canada	496	0.08	Univ Amsterdam	150	0.09	3,146	20.97	50	880	17.6
10	Spain	339	0.11	Univ Oxford	147	0.05	3,193	21.72	52	859	16.52

Figure 4 The distribution of countries/regions and institutions. The network map of institutions that are actively involved in AS research within countries/regions. AS, ankylosing spondylitis.

index standard as extremely frequent terms. *Table 4* lists 47 extremely frequent terms extracted from the retrieved literature. The cumulative percentage was 40.37% (7,452/18,459). *Table 5* shows the extremely frequent major MeSH terms/MeSH subheading terms-source articles matrix. gCLUTO was used to reset the rows of the initial matrix to aggregate similar rows in the same cluster so that 47 terms were divided into 8 clusters with biclustering, and each cluster showed the main terms contained in the source articles. We analyzed the typical articles in each cluster and summarized the topics of each cluster as follows:

❖ Surgical treatment of AS (Cluster 0);
❖ Anti-TNF inhibitor treatment for AS (Cluster 1);
❖ Correlation between endoplasmic reticulum aminopeptidase 1 (ERAP1) polymorphism and AS (Cluster 2);
❖ MRI diagnosis for AS (Cluster 3);
❖ HLA-B27 pathogenesis of AS (Cluster 4);
❖ Certain TNF inhibitors as a first-line treatment of AS, and their efficacy and safety (Cluster 5);
❖ Early diagnosis and therapy of AS (Cluster 6);
❖ Rehabilitation treatment of AS (Cluster 7).
❖ The biclustering results are presented in the form

Page 6 of 15

Liang et al. Research hotspots analysis of AS
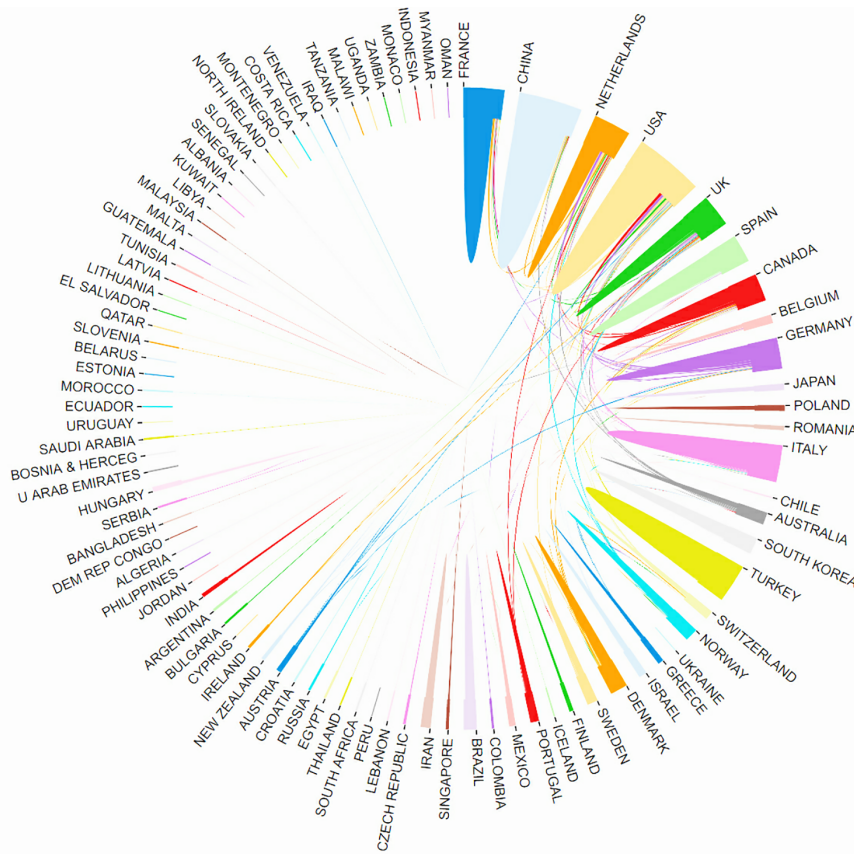
Figure 5 The distribution of countries/regions and institutions. The cooperation of countries/regions.

Table 2 The top 10 most active journals that published articles in ankylosing spondylitis (AS) research (sorted by count)

Rank	Journal title	Article counts	Percentage (N/6,818)	IF [2018]	Quartile in category [2018]	H-index	Total number of citations	Average number of citations
1	*Journal of Rheumatology*	360	0.052801408	3.634	Q2	49	3,242	9.01
2	*Clinical Rheumatology*	345	0.050601349	2.293	Q3	39	1,594	4.62
3	*Annals of the Rheumatic Diseases*	332	0.048694632	14.299	Q1	121	12,119	36.5
4	*Rheumatology International*	306	0.044881197	2.2	Q3	35	1,608	5.25
5	*Clinical and Experimental Rheumatology*	266	0.039014374	3.238	Q2	43	1,615	6.07
6	*Rheumatology*	234	0.034320915	5.149	Q1	64	2,058	8.79
7	*Arthritis Research & Therapy*	195	0.028600763	4.148	Q2	60	1,988	10.19
8	*Arthritis Care & Research*	129	0.018920505	4.53	Q2	56	1,338	10.37
9	*PLoS One*	115	0.016867116	2.776	Q2	176	445	3.87
10	*Joint Bone Spine*	113	0.016573775	3.278	Q2	34	762	6.74

Table 3 The top 10 most productive authors and co-cited authors that contributed to publications in ankylosing spondylitis (AS) research

Rank	Author	Article counts	Centrality	Total number of citations	Average number of citations	First author counts	First author citation counts	Average first author citation counts	Corresponding author	Corresponding author citation counts	Co-cited author	Citation counts	Centrality
1	Van Der Heijde	208	0.07	7,713	37.08	24	1,012	42.17	37	1,625	Braun	2,119	0.22
2	Sieper	182	0.03	8,261	45.39	30	1,357	45.23	55	2,471	Vanderlinden	1,918	0.05
3	Braun	173	0.04	7,059	40.8	34	849	24.97	47	1,255	Rudwaleit	1,522	0.12
4	Dougados	162	0.05	6,038	37.27	19	642	33.79	24	770	Van Der Heijde	1,489	0.25
5	Maksymowych	124	0.06	4,997	40.3	30	680	22.67	39	799	Sieper	1,289	0.06
6	Inman	98	0.04	2,663	27.17	4	48	12	29	375	Calin	1,174	0.11
7	Landewe	97	0.03	4,989	51.43	6	233	38.83	8	500	Dougados	1,109	0.07
8	Baraliakos	96	0.01	3,363	35.03	30	546	18.2	21	157	Garrett	1,077	0.02
9	Brown	91	0.03	2,539	27.9	8	158	19.75	39	1,221	Maksymowych	869	0.03
10	Rudwaleit	83	0.01	5,119	61.67	15	2,223	148.2	22	2001	Baraliakos	722	0.08

Figure 6 The distribution of authors engaged in AS research. The network map of productive authors. AS, ankylosing spondylitis.
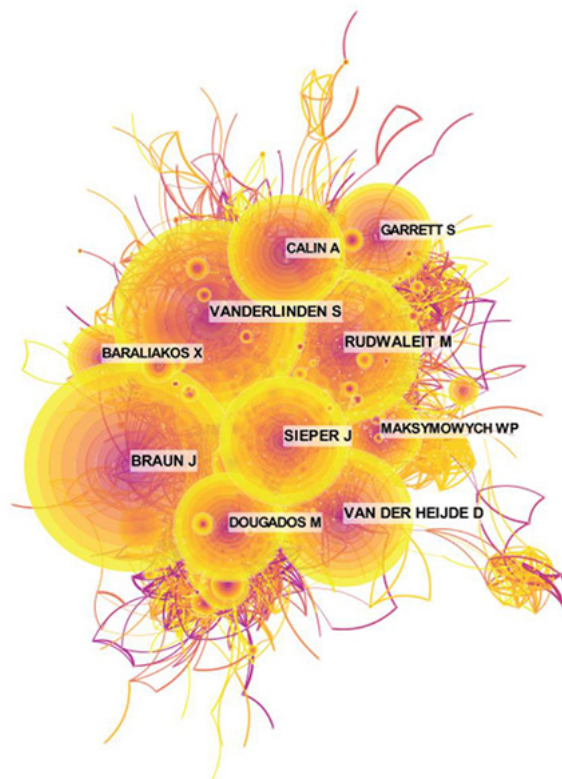
Figure 7 The distribution of authors engaged in AS research. The network map of co-cited authors. AS, ankylosing spondylitis.

Page 8 of 15

Liang et al. Research hotspots analysis of AS

Table 4 High-frequency major MeSH terms from the included publications on ankylosing spondylitis (AS) (n=18,459)

Rank	Major MeSH terms/MeSH subheadings	Frequency	Proportion of frequency (%)	Cumulative percentage (%)
1	Spondylitis, Ankylosing/drug therapy	903	4.8919	4.8919
2	Spondylitis, Ankylosing/complications	531	2.8766	7.7686
3	Spondylitis, Ankylosing/genetics	495	2.6816	10.4502
4	Spondylitis, Ankylosing/diagnosis	456	2.4703	12.9205
5	Tumor Necrosis Factor-alpha/antagonists & inhibitors	404	2.1886	15.1092
6	Antirheumatic Agents/therapeutic use	387	2.0965	17.2057
7	Spondylitis, Ankylosing/physiopathology	283	1.5331	18.7388
8	Antibodies, Monoclonal/therapeutic use	224	1.2135	19.9523
9	Spondylitis, Ankylosing/diagnostic imaging	222	1.2027	21.1550
10	Spondylitis, Ankylosing/immunology	207	1.1214	22.2764
11	Spondylitis, Ankylosing/therapy	197	1.0672	23.3436
12	Spondylitis, Ankylosing/blood	192	1.0401	24.3838
13	Spondylitis, Ankylosing/epidemiology	186	1.0076	25.3914
14	Spondylitis, Ankylosing/pathology	171	0.9264	26.3178
15	Spondylitis, Ankylosing/surgery	161	0.8722	27.1900
16	Arthritis, Rheumatoid/drug therapy	155	0.8397	28.0297
17	HLA-B27 Antigen/genetics	130	0.7043	28.7340
18	Spondylitis, Ankylosing/metabolism	116	0.6284	29.3624
19	Severity of Illness Index	115	0.6230	29.9854
20	Genetic Predisposition to Disease	105	0.5688	30.5542
21	Polymorphism, Single Nucleotide	105	0.5688	31.1230
22	Quality of Life	99	0.5363	31.6594
23	Arthritis, Psoriatic/drug therapy	96	0.5201	32.1794
24	Spondylitis, Ankylosing/psychology	95	0.5147	32.6941
25	Antirheumatic Agents/adverse effects	90	0.4876	33.1816
26	Spondylitis, Ankylosing	83	0.4496	33.6313
27	Immunoglobulin G/therapeutic use	78	0.4226	34.0538
28	Receptors, Tumor Necrosis Factor/therapeutic use	76	0.4117	34.4656
29	Kyphosis/surgery	74	0.4009	34.8665
30	Anti-Inflammatory Agents, Non-Steroidal/therapeutic use	72	0.3901	35.2565
31	Antibodies, Monoclonal/adverse effects	71	0.3846	35.6412
32	Osteotomy/methods	65	0.3521	35.9933
33	Aminopeptidases/genetics	64	0.3467	36.3400

Table 4 (*continued*)

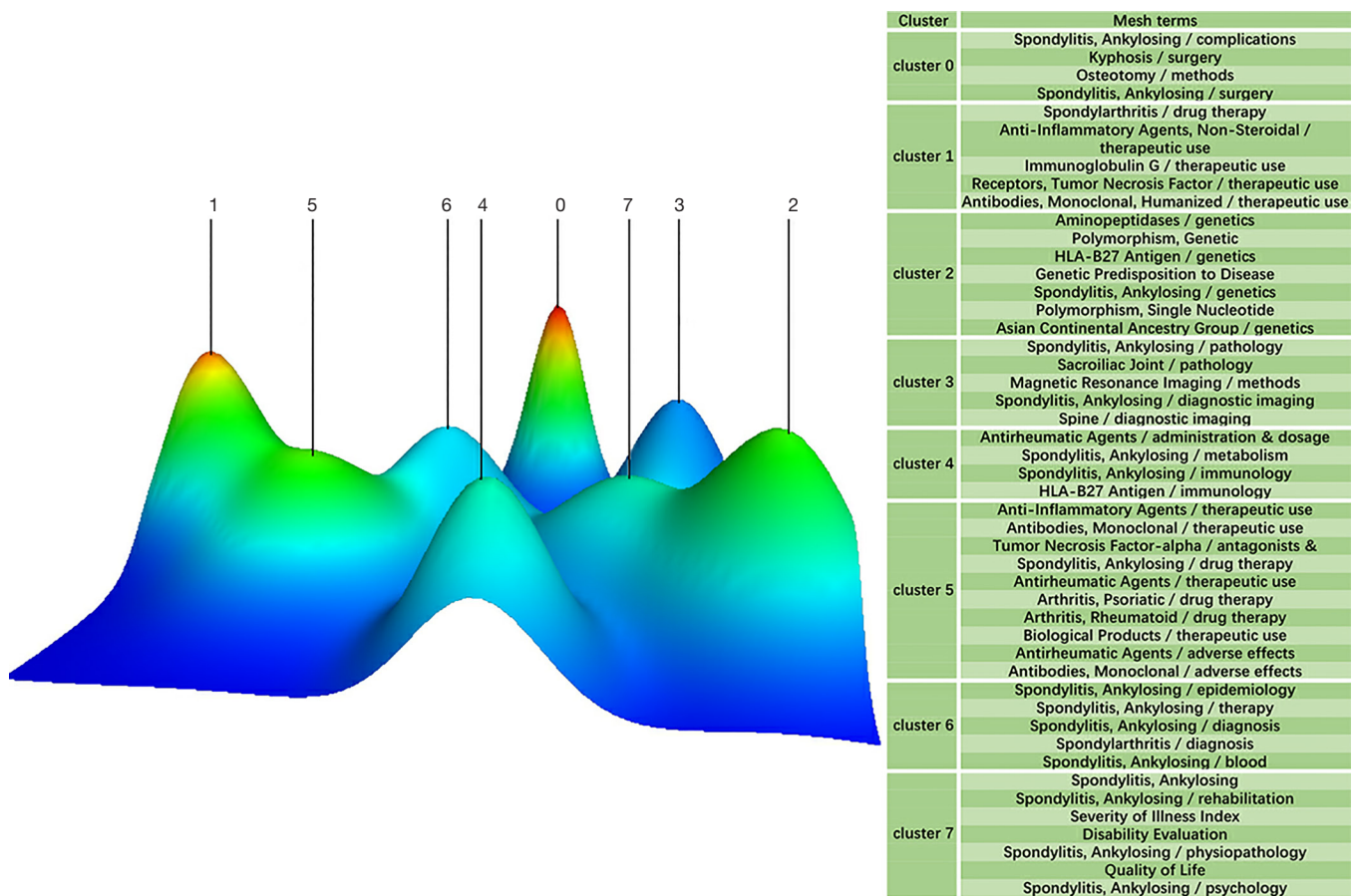**Table 4** (*continued*)

Rank	Major MeSH terms/MeSH subheadings	Frequency	Proportion of frequency (%)	Cumulative percentage (%)
34	Spondylitis, Ankylosing/rehabilitation	61	0.3305	36.6705
35	Spondylarthritis/drug therapy	59	0.3196	36.9901
36	Disability Evaluation	57	0.3088	37.2989
37	Anti-Inflammatory Agents/therapeutic use	57	0.3088	37.6077
38	Spondylarthritis/diagnosis	55	0.2980	37.9056
39	Spine/diagnostic imaging	55	0.2980	38.2036
40	Sacroiliac Joint/pathology	54	0.2925	38.4961
41	Antirheumatic Agents/administration & dosage	53	0.2871	38.7832
42	Magnetic Resonance Imaging/methods	50	0.2709	39.0541
43	HLA-B27 Antigen/immunology	49	0.2655	39.3196
44	Antibodies, Monoclonal, Humanized/therapeutic use	49	0.2655	39.5850
45	Asian Continental Ancestry Group/genetics	49	0.2655	39.8505
46	Biological Products/therapeutic use	48	0.2600	40.1105
47	Polymorphism, Genetic	48	0.2600	40.3706

Table 5 High-frequency major MeSH in a terms-source articles matrix (localized)

No.	Major MeSH terms/MeSH subheadings	PubMed Unique Identifiers of source articles				
		18375542	18390569	18495735	…	31383427
1	Spondylitis, Ankylosing/drug therapy	1	0	1	…	0
2	Spondylitis, Ankylosing/complications	0	0	0	…	0
3	Spondylitis, Ankylosing/genetics	0	0	0	…	0
4	Spondylitis, Ankylosing/diagnosis	0	0	0	…	0
…	…	…	…	…	…	…
45	Asian Continental Ancestry Group/genetics	0	0	0	…	0
46	Biological Products/therapeutic use	0	0	0	…	0
47	Polymorphism, Genetic	0	0	0	…	0

Page 10 of 15

Liang et al. Research hotspots analysis of AS

Cluster	Mesh terms
cluster 0	Spondylitis, Ankylosing / complications
	Kyphosis / surgery
	Osteotomy / methods
	Spondylitis, Ankylosing / surgery
cluster 1	Spondylarthritis / drug therapy
	Anti-Inflammatory Agents, Non-Steroidal / therapeutic use
	Immunoglobulin G / therapeutic use
	Receptors, Tumor Necrosis Factor / therapeutic use
	Antibodies, Monoclonal, Humanized / therapeutic use
cluster 2	Aminopeptidases / genetics
	Polymorphism, Genetic
	HLA-B27 Antigen / genetics
	Genetic Predisposition to Disease
	Spondylitis, Ankylosing / genetics
	Polymorphism, Single Nucleotide
	Asian Continental Ancestry Group / genetics
cluster 3	Spondylitis, Ankylosing / pathology
	Sacroiliac Joint / pathology
	Magnetic Resonance Imaging / methods
	Spondylitis, Ankylosing / diagnostic imaging
	Spine / diagnostic imaging
cluster 4	Antirheumatic Agents / administration & dosage
	Spondylitis, Ankylosing / metabolism
	Spondylitis, Ankylosing / immunology
	HLA-B27 Antigen / immunology
cluster 5	Anti-Inflammatory Agents / therapeutic use
	Antibodies, Monoclonal / therapeutic use
	Tumor Necrosis Factor-alpha / antagonists &
	Spondylitis, Ankylosing / drug therapy
	Antirheumatic Agents / therapeutic use
	Arthritis, Psoriatic / drug therapy
	Arthritis, Rheumatoid / drug therapy
	Biological Products / therapeutic use
	Antirheumatic Agents / adverse effects
	Antibodies, Monoclonal / adverse effects
cluster 6	Spondylitis, Ankylosing / epidemiology
	Spondylitis, Ankylosing / therapy
	Spondylitis, Ankylosing / diagnosis
	Spondylarthritis / diagnosis
	Spondylitis, Ankylosing / blood
cluster 7	Spondylitis, Ankylosing
	Spondylitis, Ankylosing / rehabilitation
	Severity of Illness Index
	Disability Evaluation
	Spondylitis, Ankylosing / physiopathology
	Quality of Life
	Spondylitis, Ankylosing / psychology

Figure 8 Mountain visualization depicting biclustering of high-frequency major MeSH terms and literature on AS. AS, ankylosing spondylitis.

of mountain visualization (*Figure 8*) and matrix visualization (*Figure 9*).

The mountain visualization in *Figure 8* shows the 8 clusters from 0 to 7 after biclustering and the extremely frequent terms contained in each cluster. The biclustering results and the nature of the high-dimensional datasets can be intuitively expressed through mountain visualization. In *Figure 8*, each peak represents a different cluster. The position, height, color, and volume of the peaks on the plane can reflect the information of the clusters, of which the position of the peaks on the plane is most significant when compared with other peaks. The interval between the peaks can indicate the relative similarity of the clusters. The height of the peak often represents the internal similarity in the cluster. The color of the peak shows the internal standard deviation of the objects in each cluster: blue indicates a high deviation, and red indicates a low deviation. The volume of each peak is proportional to the number of

extremely frequent terms stored in the cluster. There was a minimum of 30 publications per cluster. We ruled out results with three-peaked peaks.

Figure 9 shows the matrix visualization, with extremely frequent major MeSH terms/MeSH subheading terms as row labels and the PMIDs of the source articles as the column labels. The color depth of the blocks which were proportional to the frequency of the terms in the articles represented the values; the darker the color, the greater the significance. White means almost no significance. The relationships between the source articles are shown in the cluster tree above. The relationships among extremely frequent major MeSH terms/MeSH subheading terms are shown in the cluster tree on the left.

Discussion

As the incidence of orthopedic diseases increases year by
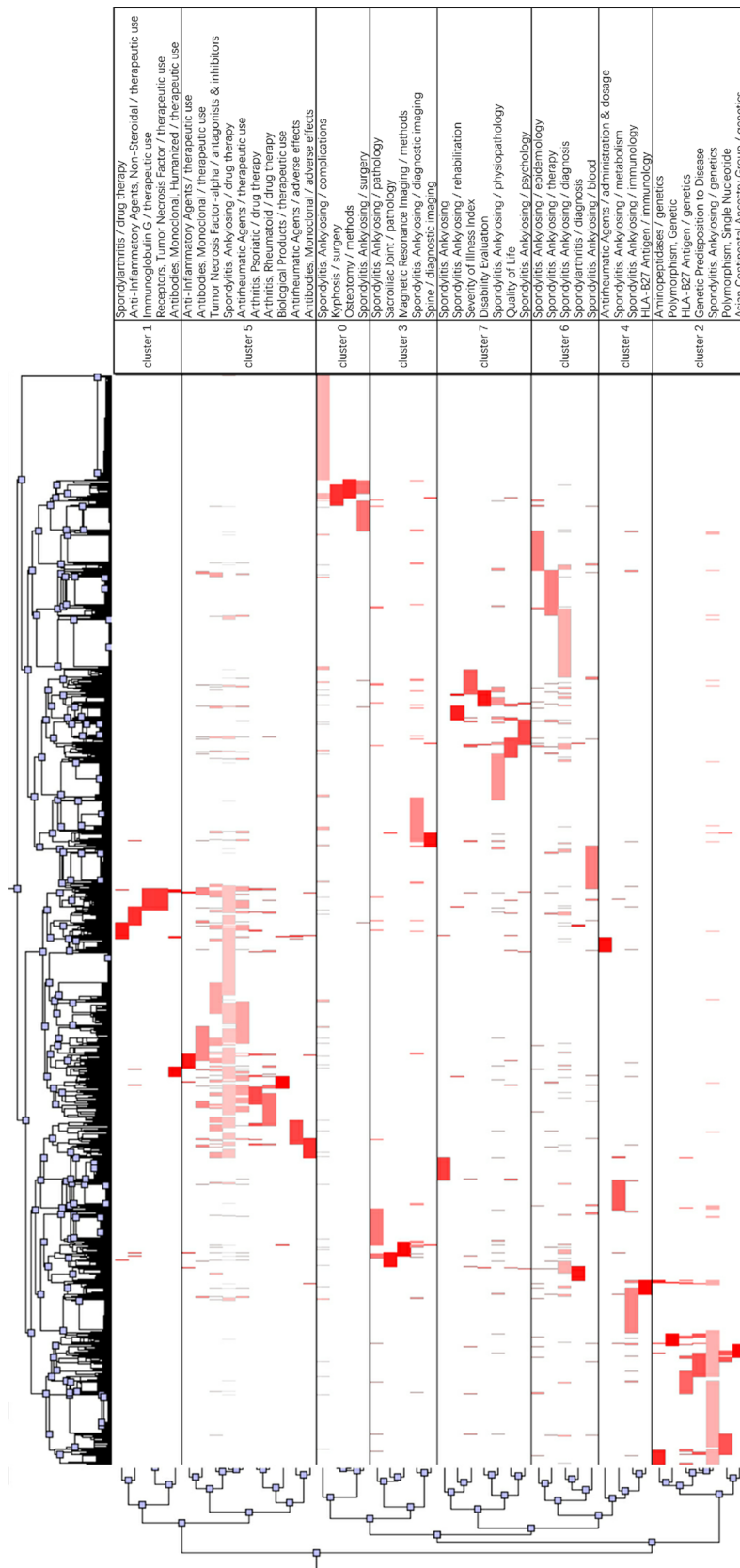
Figure 9 Visualized matrix depicting biclustering of high-frequency major MeSH terms and PubMed Unique Identifiers (PMIDs) of literature on AS. AS, ankylosing spondylitis.

Page 12 of 15

Liang et al. Research hotspots analysis of AS

year, and the amount of scientific literature in related fields increases dramatically, making it difficult to keep up to date with the latest research in real time. For this reason, bibliometrics has become an important method of analyzing and displaying the developing trends in disease research. In this study, we found an increasing trend in the literature on AS over the 10 years between 2009 and 2018, and found 8 hotspots in AS research.

Cluster 0 relates to the surgical treatment of AS. As the disease progresses, severe AS can cause complications, such as visceral compression and impaired respiratory function. Surgery is necessary to correct the deformity to reduce symptoms and prevent serious complications. A study by Fu *et al.* demonstrated that pedicle subtraction osteotomy can improve pulmonary function in patients with AS kyphosis (13). A previous study also showed that corrective osteotomy is an effective surgical strategy for treating AS with kyphosis deformity (14). There are several basic osteotomy strategies, among which Zheng *et al.* suggested that for severe thoracolumbar kyphotic deformity, interrupted 2-level spinal osteotomy is the most effective (15). Determining the exact surgical correction angle is also important. A study by Song *et al.* provided a new method for calculating the precise angle required for spinal osteotomy, which can provide accurate and replicable calculations for AS correction (16). Due to the pathological characteristics of AS, AS patients are extremely susceptible to spinal fractures, which often lead to severe consequences. Given that AS is often accompanied by damage to other organs throughout the body, especially the respiratory organs, there can be many surgical complications and risks, leading to high mortality. Early literature in the field recommended conservative treatment. However, in recent years, with the continuous advancement of anesthesia technology and surgical techniques, a growing body of evidence suggests that surgical treatment can better stabilize the spine. Furthermore, surgery can directly relieve nerve compression and be more effective in avoiding complications caused by long-term traction and external fixation. Therefore, for patients with AS combined with spinal fractures, as long as the patient's physical condition allows, surgical treatment is feasible. However, for patients with certain comorbidities, choosing the appropriate surgical method is extremely important. Therefore, the classification of AS spinal fractures and the choice of fixation orthopedics are hotspots for future AS treatment.

Cluster 1 relates to TNF inhibitors as a treatment for AS. TNF inhibitors are the first biologics used to treat AS and are suitable for all stages of AS, especially for patients who have failed NSAIDS treatment or who cannot tolerate the side effects of NSAIDs. Not only can TNF inhibitors alleviate peripheral inflammation, but they can reduce pain by acting on the central nervous system (17) and can also inhibit the radiological progress of the spine (18). Furthermore, long-term TNF inhibitor treatment can slow down the development of new lesions, especially when treatment is initiated at the early stages of the disease. Since TNF inhibitors have demonstrated efficacy in the treatment of AS, future research should continue to examine the role of TNF inhibitors across the disease course of AS, and explore how to increase their sensitivity.

Cluster 2 relates to the correlation between the *ERAP1* polymorphism and AS. *ERAP1*, unlike HLA-B27, is a non-major histocompatibility complex (*MHC*) gene, located on chromosome 5q15, which has been associated with AS (19). ERAP1 can trim peptides to the optimal length for class I HLA presentation for recognition by immune cells. *ERAP1* single nucleotide polymorphisms (SNPs) affect ERAP1 enzymatic properties, further affecting peptide presentation by HLA-B27 molecules. Because the frequency of alleles is not the same between different populations, the correlation between the *ERAP1* polymorphism and AS is also different. Lee *et al.* and Zhang *et al.* have separately revealed that polymorphisms of *ERAP1* are associated with AS susceptibility in Europeans and Beijing Han (20,21). *ERAP1* gene variants have also been shown to be associated with HLA-B27 positive spondyloarthritis in Romania (22). The discovery of *ERAP1* compensates for AS pathogenesis that HLA-B27 cannot fully explain. Since *ERAP1* polymorphisms are associated with AS in a variety of populations, further studies on associations in specific populations are needed to determine whether *ERAP1* polymorphisms are related to disease severity.

Cluster 3 relates to MRI diagnosis of AS. Imaging plays an important role in diagnosing AS. MRI demonstrating sacroiliitis has been included as an effective imaging criteria for AS by ASAS for the first time (23). MRI can detect active and structural changes more sensitively several years before conventional radiography, making it an ideal imaging method for the early diagnosis of axial spondyloarthritis (SpA) or AS (24). Akar *et al.* also revealed that a positive MRI result was an important risk factor for radioactive sacroiliitis (25), which may progress into AS. An MRI can significantly increase doctors' confidence in diagnosing axial SpA, which was shown to cause up to 40%

of people to change their treatment plan and start using biological agents (26). In conclusion, using MRI as early as possible is essential in helping patients to receive anti-TNF treatment early. Researchers should also focus more on the application value of MRI compared to traditional imaging in AS diagnosis, and explore more accurate MRI diagnostic criteria.

Cluster 4 relates to the HLA-B27 pathogenesis of AS. The human leukocyte antigen class I gene HLA-B27 has a strong correlation with AS. Over 90% of AS patients carry the *HLA-B27* gene, while the proportion of HLA-B27-positive healthy individuals is less than 10% (27). Accorinti *et al.* confirmed that there was a strong association between HLA-B27, uveitis and AS. Normally, uveitis precedes the onset of rheumatism (28), which suggests that HLA-B27 has a significant correlation with AS. In recent years, the newly discovered *ERAP1* and *ERAP2* have filled the gap in the pathogenesis of AS. B27 peptidome formation is a key event in AS. Martín-Esteban *et al.* suggested that the HLA-B27 peptidome in AS pathogenesis can be affected by different ERAP1/ERAP2 phenotypes (29). Overall, although the association between HLA-B27 and AS has long been demonstrated, the exact role of HLA-B27 in the onset of AS is still elusive. In the future, further exploration into the role of HLA-B27 and its association with non-MHC factors like ERAP are needed to more comprehensively understand AS pathogenesis, which will be the largest research hotspot in AS.

Cluster 5 relates to certain TNF inhibitors as a first-line treatment for AS, and their efficacy and safety. There are five common TNF inhibitors for AS: infliximab, adalimumab, golimumab, etanercept, and certolizumab. The first three are full-length monoclonal antibodies, etanercept is a soluble fusion protein, and certolizumab is a humanized fragment antigen-binding fragment. Although they are all TNF inhibitor drugs, they are not the same in terms of drug safety and survival rate, and their efficacy and application are also different. Hence, when one of the drugs is not effective, it is usually replaced with another drug for treatment. This was confirmed by Rudwaleit *et al.*, who demonstrated that switching to adalimumab after previous TNF antagonist treatment could improve the AS disease status. Furthermore, the safety profile was the same as that of patients who were anti-TNF treatment naïve or treated with adalimumab alone (30). Kay *et al.* also assessed the 5-year golimumab safety profile, revealing that subcutaneous golimumab safety at year 5 was consistent with the previously reported year 3 as well as with other

TNF antagonist treatments (31). Favalli *et al.* compared the real-world 10-year retention rate of first-line anti-TNF drugs and withdrawal rates between adult and juvenile patients, demonstrating that etanercept showed the highest drug survival in an adult-onset population and infliximab the lowest in a juvenile-onset population (32). Due to the diversity of drugs and disease populations, more clinical trials are required to further clarify the safety and efficacy of each TNF antagonist.

Cluster 6 relates to the early diagnosis and therapy of AS. Axial spondyloarthritis (axSpA) includes non-radiological axSpA (nraxSpA) and radiological axSpA (namely, AS). Since patients with nraxSpA have similar clinical characteristics to those with confirmed AS, Rumyantseva *et al.* proposed that the former can be imagined as the early stage of AS (33). Due to different clinical manifestations and limited knowledge among general practitioners (GPs), axSpA is often diagnosed with a delay (34), which may lead to a more severe prognosis. Therefore, in order to diagnose AS early, educating GPs is important (35). Early identification of patients who may suffer from axSpA, along with effective treatment, can improve the functional status and quality of life for patients and may inhibit disease progression.

Cluster 7 relates to the rehabilitation treatment of AS. Researchers have demonstrated that comprehensive rehabilitation is beneficial for improving the quality of life of AS patients (36). Therefore, an effective method for assessing patient status is of great importance. Ankylosing spondylitis Quality of Life (EASi-QoL) is more effective than other QoL measures (37), and includes four aspects: physical function (PF), disease activity (DA), emotional well-being (EWB) and social participation (SP). Among these, PF and DA are the main factors that determine the patient's physical health (38). Structured education also has a positive effect on patient rehabilitation (39). Therefore, the participation of AS patients in rehabilitation and education is of vital importance.

Conclusions

Our study identified eight research hotspots in the field of AS, predicting surgical treatment and etiology as the main research trends in the future. The classification of spinal fractures in AS, the selection of corresponding internal fixation and osteotomy methods, and postoperative efficacy need to be further studied. Furthermore, the roles of HLA-B27 and ERAP in the pathogenesis of AS remain unclear, which provides new directions and ideas for future research.

Page 14 of 15

Liang et al. Research hotspots analysis of AS

Acknowledgments

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-20-1259). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Ethical approval is not required because the research didn't involve human experiments.

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