Dermatology Practical & Conceptual

Knowledge Structure and Trends of Vitiligo From 2002 to 2023: A Bibliometric Analysis

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ABSTRACT

Introduction: Vitiligo is a common acquired depigmenting dermatosis resulting from a loss of epidermal melanocytes. The academic attention to vitiligo has gradually increased over the past two decades.

Objective: We aimed to explore the current research structure and trends of vitiligo.

Methods: Publications about vitiligo from the Web of Science Core Collection (WoSCC) database were searched. VOSviewer, CiteSpace, GraphPad Prism 8, ArcGIS, and Charticulator were implemented for data description and visual analysis.

Results: A total of 3,037 publications authored by 10,993 individuals from 2,753 institutions across 88 countries/regions were collected. These publications were published in 616 journals and cited a total of 39,433 references. China was the most productive country. Cairo University and Ezzedine Khaled were the most prolific institution and author, respectively. Additionally, the *British Journal of Dermatology* stood out as the journal with the highest number of publications. According to the analysis of keywords and references, “quality of life,” “depression,” and “validation” were hotspots in terms of clinical characteristics, while “prevalence”, “comorbidity,” “association,” and “immunotherapy” gained more research interest with respect to epidemiology and genetics. The frontiers of pathogenesis focused on “unfolded protein response,” “migration,” “biomarkers,” and “CXCL10.” As far as treatment is concerned, there was increasing attention to “janus kinase inhibitor,” “fractional carbon dioxide laser,” “platelet-rich plasma,” and “5-fluorouracil.”

Conclusion: The bibliometric analysis elucidates the foundational knowledge structure on research forces and unveiled the hotspots and frontiers, aiding researchers in gaining a deeper comprehension of the future development trends in the field of vitiligo.

Introduction

Vitiligo is an autoimmune disease characterized by depigmentation macules or patches on the skin resulting from a loss of epidermal melanocytes, with an estimated global prevalence of 0.5%–2.0% [1-3]. Vitiligo is often misunderstood as a cosmetic disorder due to its lack of direct menace to the life of patients. However, the white lesions, particularly on exposed areas, can heavily burden daily life and even lead to devastating psychological and mental problems.

Taking literature as the research object, bibliometrics is a quantitative analysis method that employs mathematical and statistical techniques to examine the structure, characteristics, and rules of scientific research [4, 5]. In a previous study, 7,187 publications on vitiligo from 1975 to 2017 were searched in four databases [6]. The findings systematically described the publication situation, main research forces, and their co-occurrence networks in the field of vitiligo. However, that study did not delve into the understanding of the knowledge base and evolution of vitiligo. Based on publications collected from the WoSCC, we conducted visual analysis of various aspects, including outputs, countries/regions, institutions, authors, journals, keywords, and references.

Objective

Our goal was to describe the current knowledge structure, hotspots, and frontiers in the field of vitiligo over the past two decades, which can provide knowledge support for future research and management.

Methods

Data Sources and Collection

In this study, we selected the WoSCC for data retrieval. The WoSCC is a high-quality database covering comprehensive publications from different fields and is regarded as one of the most appropriate databases for bibliometric analysis [7-8]. Data were retrieved on a single day, May 28, 2024. The search strategy was as follows: TI = vitiligo. Searching only by titles is considered a retrieval method which obtains more relevant data [9]. Only articles and review articles written in English and published between 2002 and 2023 were included. After standardizing data and removing potential duplicates through CiteSpace, a total of 3,037 publications were included in this analysis.

Data Analysis and Visualization

VOSviewer (version 1.6.18) is an available computer program for bibliometric visualization [10]. It is used to construct distance-based maps where distance between two nodes reflects the strength of the relation mutually, which makes it easy to cluster items with strong correlation. In this study, VOSviewer was applied to visualize co-authorship of institutions and authors and co-occurrences of keywords.

CiteSpace (version 6.3.R1) is a Java-based application which can present the structure, rules, and distribution of scientific knowledge by means of visualization [11-12]. Co-citation analysis is the one of its bright spots, allowing the grouping of frequently co-cited references into a single cluster. Dual-map overlay of journals displays the distribution and citation trajectory of each subject of publications [13]. Furthermore, burst detection can be adapted to detect sharp increases in interest. In this study, CiteSpace was used to visualize dual-map overlay of journals, co-citation of references, and burst detection of keywords and references.

In addition, GraphPad prism 8 (version 8.0.2) and ArcGIS (version 10.8.1) were employed for the visualization output and for spatial distribution of publications, respectively. Also, Chaticulator was applied to depict a chord diagram concerning collaboration of countries/regions.

Results

Publication Output Trends on Vitiligo

A total of 3,037 publications were included in the analysis. Increasing attention was paid to vitiligo over the past two decades (Figure 1A). The annual publications increased from 42 in 2002 to 296 in 2023, with an annual growth rate of 9.74%.

Analysis of Countries/Regions

The 3,037 publications were published in 88 countries/regions. As shown in Figure 1B, there was global interest in vitiligo research. The top 10 productive countries are listed in Table S1. China had 568 publications, ranking first, followed by the USA (472), and India (385). The USA had 17,254 citations, exceeding other countries/regions. However, when it came to the citations per publication (C/P), France ranked first (54.71). Figure 1C shows the international cooperation among the top 36 countries/regions divided into six clusters. The USA, France, and Italy were the top three countries in terms of total link strength (TLS). Furthermore, these countries had the maximum TLS in their respective clusters. TLS is the number of co-occurrences between two nodes, indicating the cooperative communication relationship.

Analysis of Institutions

Overall, 2,753 institutions participated in the research on vitiligo. Table S2 lists the top 10 productive institutions. Cairo University had the greatest number of publications (103), followed by the Post Graduate Institute of

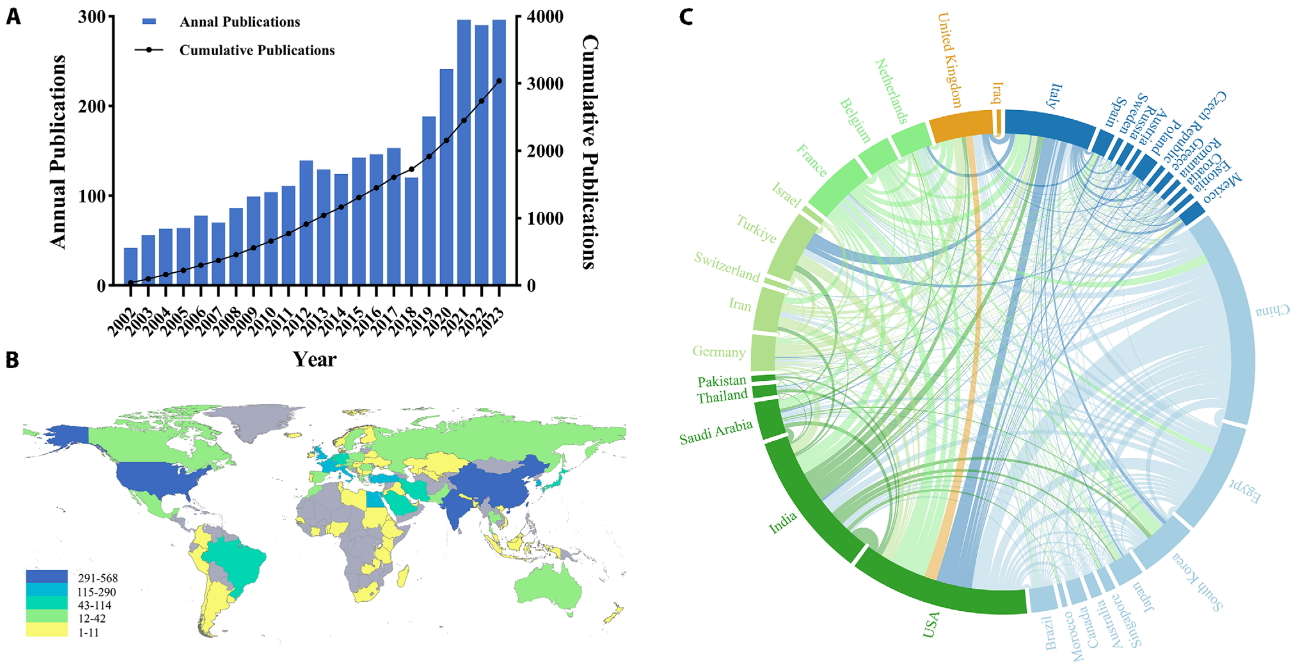

Figure 1. Publication output trends and analysis of countries/regions on vitiligo. (A) Trends of publication output from 2002 to 2023. The number of annual publications fluctuated between 42 and 296, with a maximum number in 2023. An overall uptrend in annual publications was observed. (B) Spatial distribution of publications according to countries/regions. The yellow-to-blue represents an increasing number of publications. The grey represents countries/regions with no publications. (C) International cooperation between top 36 countries/regions which had more than 10 publications. The nodes of different colors represent the countries/regions with different clusters. The width of node represents the number of publications, while the width of the arc links indicates the strength of the connection between countries/regions.

Medical Education & Research (89), and Ghent University Hospital (78). It was interesting that despite Cairo University's having the most abundant output, its number of C/P was lower than that of other top 10 productive institutions. Figure 2A shows the co-authorship network between the top 52 institutions grouped into eight clusters. Notably, there were five clusters corresponding to specific countries respectively. These countries included China (blue cluster), Egypt (yellow cluster), South Korea (purple cluster), India (brown cluster), and Iran (orange cluster). In Figure 2B, the color of a node is related to the average publication year (APY). Therefore, institutions whose node color is close to yellow will continue to be dominant and influential in the future.

Analysis of Authors

Generally, 10,993 authors contributed to the 3,037 publications. Table S3 lists the top 10 productive authors. Ezzedine Khaled published 85 articles, ranking first, followed by Van Geel N (79) and Parsad Davinder (78). Among the top 10 productive authors, eight were affiliated with the aforementioned top 10 productive institutions. Ezzedine Khaled had the most citations and the highest H index score. Figure 2C shows the network visualization map between 48 authors. It was noted that Ezzedine Khaled, Taieb Alain, and Seneschal Julien were grouped into the yellow cluster, Van Geel, Parsad Davinder, Hamzavi Iltefat, and Wolkerstorfer Albert grouped into the red cluster, while Li Chunying and Gao Tianwen grouped into the blue cluster, which indicates that most of the top productive authors had close cooperation. We also conducted a co-authorship overlay map of authors which showed their academic active periods (Figure 2D).

Analysis of the Most Productive Journals

The 3,037 articles were published in 616 journals. The top 10 productive journals are listed in Table S4. The *British Journal of Dermatology* ranked first, with 126 publications. Another notable journal was the *Journal of the American Academy of Dermatology*, which received the largest number of C/P (56.28) and had the highest IF (12.8). It was noticeable that eight journals were classified as Q1 according to the Journal Citation Report, and the output of the top 10 journals accounted for 31.81% total, which indicates their leading role in the research of vitiligo. Figure 3 shows the dual-map overlay of journals concerning vitiligo. The yellow curve shows that journals in the fields of molecular/biology/immunology were influenced by molecular/biology/genetics and dermatology/dentistry/surgery. The grey curves show that journals in the fields of dentistry/dermatology/surgery were influenced by molecular/biology/genetics, dermatology/dentistry/surgery, and health/nursing/medicine. The green curve indicates that journals in the fields of medicine/medical/clinical were influenced by molecular/biology/genetics.

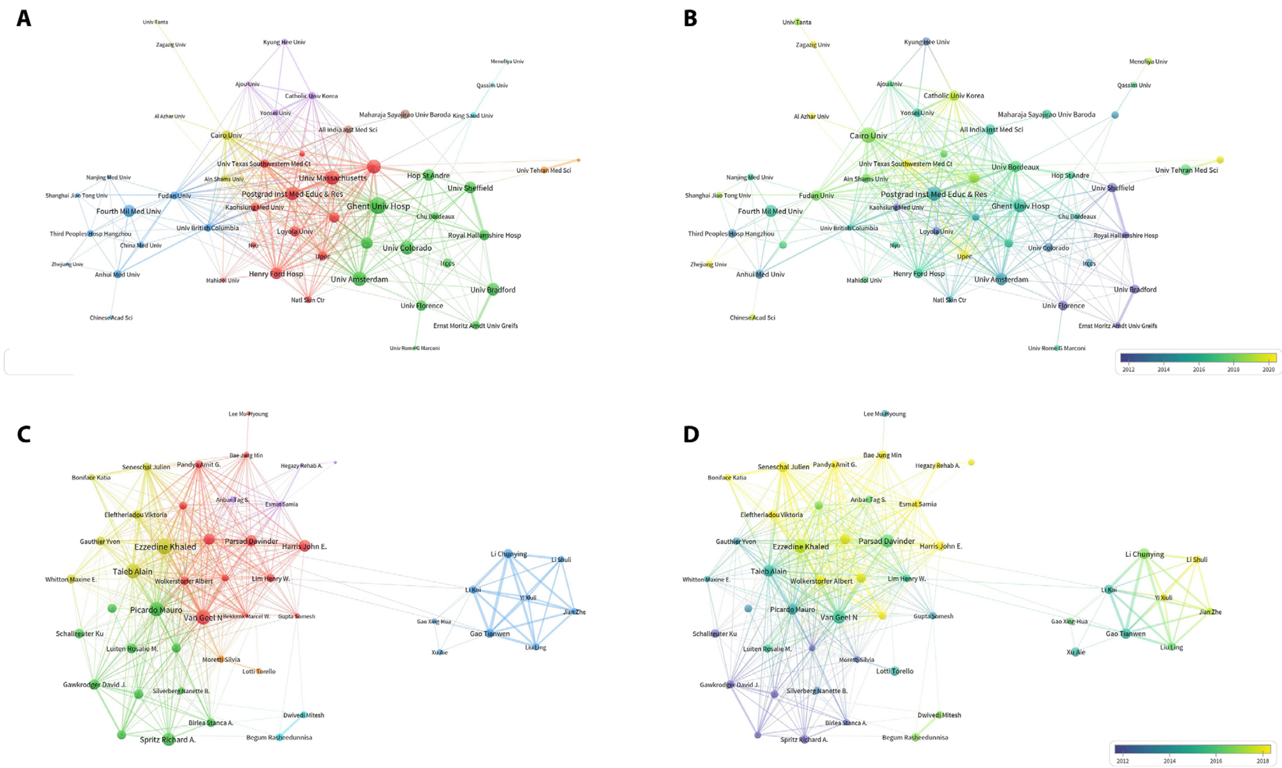

Figure 2. Analysis of institutions and authors. (A) Co-authorship network map between top 52 institutions which had more than 15 publications. The width of the links indicates link strength between two nodes. The nodes of different colors represent the institutions of different clusters, and the size represents the number of citations between institutions. (B) Co-authorship overlay map between top 52 institutions which had more than 15 publications. The color of nodes is related to the APY, and the size represents the number of publications. (C) Co-authorship network between top 48 authors who had more than 20 publications. The nodes of different colors represent the authors of different clusters, and the size represents the number of citations between authors. (D) Co-authorship overlay map between top 48 authors. The color of nodes is related to the APY, and the size represents the number of publications.

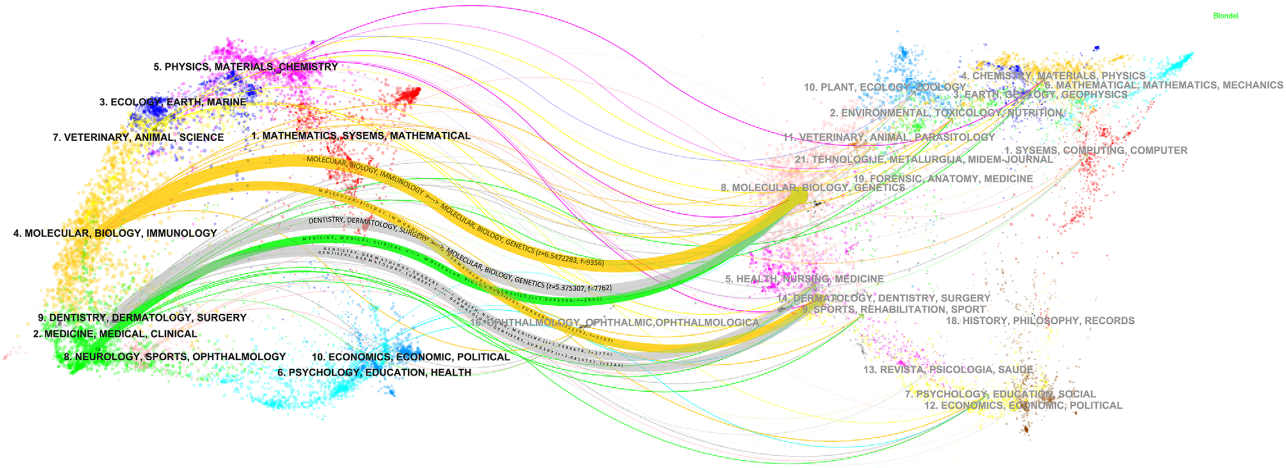

Figure 3. Dual-map overlay of journals concerning vitiligo. The citing journals are on the left, while cited journals are on the right. The curves between journals represents the citation trajectories.

Analysis of Keywords

In general, 5,697 keywords were extracted from the 3,037 publications. Figure 4A shows the network visualization map of 185 keywords. All the keywords were grouped into three clusters, each of which probably representing a topic in the field of vitiligo. The keywords belonging to the red cluster mainly addressed pathogenesis. The green cluster primarily focused on treatment, while the blue cluster contains clinical characteristics, epidemiology, and genetics. Furthermore, the overlay visualization map revealed the temporal characteristics of keywords (Figure 4B). Nodes in yellow were published in recent years, on average, indicating potential hot topics

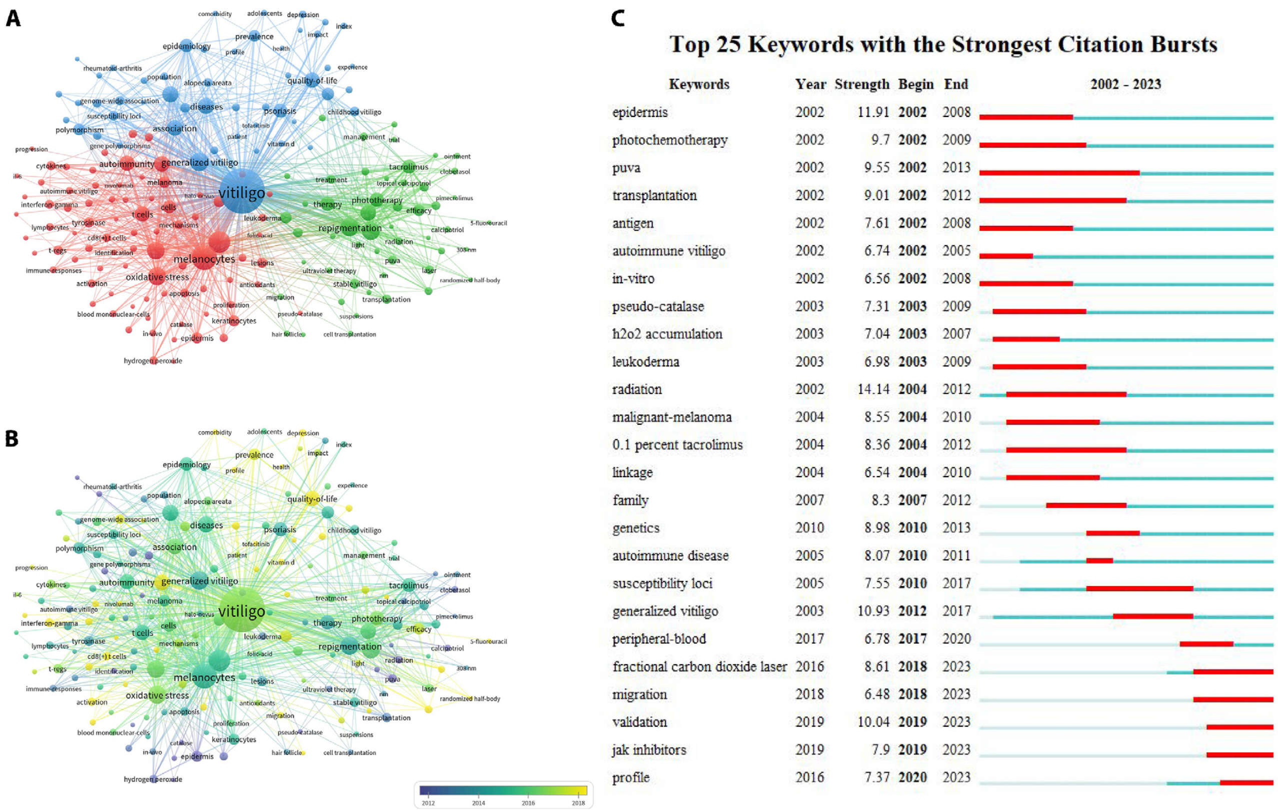

Figure 4. Analysis of keywords. (A) Co-occurrence network map between top 185 keywords which had more than 20 occurrences. The nodes of different colors represent the keywords of different clusters. The size of nodes is proportional to occurrences of keywords, while the distance between two nodes is related to association of the two keywords. (B) Co-occurrence overlay map between top 185 keywords. The color of nodes is related to the APY. (C) Top 25 keywords with the strongest citation bursts. The red bars indicate the durations of the bursts.

in the future. Table 1 lists the five most frequent keywords and the latest keywords in each cluster, including "biomarkers," "CXCL10," "unfolded protein response," "platelet-rich plasma," "5-fluorouracil," "validation," and "comorbidity." Figure 4C displays the top 25 keywords with the strongest citation bursts. Among these, the keywords "radiation," "epidermis," and "generalized vitiligo" ranked as the top three in terms of strength. These keywords highlighted the main areas of interest concerning vitiligo. In addition, the keywords "fractional carbon dioxide laser," "migration," "validation," "jak inhibitors," and "profile" have gained popularity in recent years and are expected to remain significant topics in the future.

Analysis of Co-citation on References

In summary, 39,433 references were cited by the 3,037 publications. Table S5 lists the top 10 co-citation references. An article titled "Epidemiology of vitiligo and associated autoimmune diseases in Caucasian probands and their families" ranked first, with 331 citations. It was noticeable that there were two articles published by Ezzedine Khaled, one article by Taieb Alain, and one article by Hamzavi Iltefat. These authors ranked among the top 10 productive authors, further highlighting their significant influence in academic research. Figures 5A and B show the co-citation network and clustering of the 1,299 references. Clusters #4, #8, and #13 studied the clinical characteristics of vitiligo, while clusters #1, #11, and #15 focused on epidemiology and genetics of vitiligo. Furthermore, clusters #0, #3, #5, #10, and #14 conducted research on the pathogenesis of vitiligo, while clusters #2, #6, #7, #9, and #12 primarily concentrated on the treatment of vitiligo. Figure 5B also depicts the time fluctuation of the 16 clusters, which hints that the hotspots on vitiligo have changed over time. "melanocyte" (#5) and "PUVA" (#9) were initial hotspots, while researchers are currently focusing more on "oxidative stress" (#0), "platelet-rich plasm" (#6), "jak inhibitors" (#7), and "quality of life" (#8). Figure 5C shows the top 25 references with the strongest citation burst. The article "Vitiligo," by Ezzedine Khaled and published in *The Lancet* in 2015, was highly influential and ranked among the top 10 most cited references.

Discussion

General Structure of Vitiligo Research

The analysis of research strength indicates that China and France are the dominant countries in the field. China led in terms of quantity, with two of the top 10 productive

Table 1. Top Five Most Frequent Keywords and Latest Keywords in Each Cluster.

Cluster	Rank	Keyword	Occurrences	Cluster	Rank	Keyword	AAY
Red	1	melanocytes	551	Red	1	biomarkers	2020.6444
Red	2	skin	419	Red	2	nivolumab	2020.4783
Red	3	oxidative stress	292	Red	3	CXCL10	2020.2174
Red	4	expression	267	Red	4	Unfolded protein response	2019.1389
Red	5	pathogenesis	215	Red	5	survival	2018.7727
Green	1	repigmentation	294	Green	1	platelet-rich plasma	2020.7391
Green	2	ultraviolet b	289	Green	2	fractional carbon dioxide laser	2019.5439
Green	3	narrow band uvb	217	Green	3	randomized half-body	2019.1905
Green	4	phototherapy	186	Green	4	5-fluorouracil	2019.0909
Green	5	therapy	181	Green	5	safety	2019.0400
Blue	1	vitiligo	1782	Blue	1	tofacitinib	2021.2692
Blue	2	generalized vitiligo	299	Blue	2	jak inhibitors	2021.069
Blue	3	diseases	234	Blue	3	metabolic syndrome	2020.5238
Blue	4	autoimmune disease	227	Blue	4	validation	2019.9318
Blue	5	association	222	Blue	5	comorbidity	2019.8214

Figure 5. Analysis of references. (A) Co-citation network map of 1,299 references. The size of nodes is determined by the number of co-citations, and different colors denote different years. Nodes with a purple outer ring have a larger centrality, indicating potentially revolutionary publications. (B) Clustering of 1,299 references. Nodes with highlighted links signify larger degree, which implies significant intellectual contributions as widely co-cited articles. (C) Top 25 references with the strongest citation bursts.

institutions and two of the top 10 productive authors coming from China. Nevertheless, France was qualitatively superior and had greater academic influence, as evidenced by its highest number of C/P. France also had one productive institution and three prolific scholars. Moreover, the University of Massachusetts in the USA, Ghent University Hospital in Belgium, and the University of Bordeaux in France were considered more academically influential. We also found

Table 2. Hotspots and Frontiers of Vitiligo in 4 Main Research Orientations.

Research orientation	Hotspots and frontiers
Clinical characteristics	quality of life, depression, validation
Epidemiology and genetics	prevalence, comorbidity, association, immunotherapy
Pathogenesis	unfolded protein response, migration, biomarkers, CXCL10
Treatment	JAK, fractional carbon dioxide laser, platelet-rich plasma, 5-fluorouracil

that the most prolific authors were affiliated with productive institutions and worked closely together. Among the top 10 most prolific authors, three authors were from the same institution, which further indicated the great influence of the University of Bordeaux in France. Ezzedine Khaled was the most productive author and also a prominent scholar. In addition to participating in reaching the Vitiligo Global Issues Consensus, he and his team are actively exploring new targeted and safe treatment for vitiligo via clinical trials [14-15]. When it comes to the research strength of corporate networks, we found that international collaboration was widespread. The main hubs of cooperation were the USA, France, and Italy, fostering close relationships between European countries and the USA. Furthermore, there was significant collaboration between authors within the same country or even within the same institution. This collaboration was primarily concentrated in certain Asian countries, notably China and South Korea, which continued to be dominated by domestic partnership. Moreover, the *British Journal of Dermatology,* the *Journal of Investigative Dermatology*, and the *Journal of the American Academy of Dermatology* are core journals in the field of vitiligo. The dual-map overlay revealed that the knowledge base of vitiligo consists of the fields of molecular/biology/genetics, dermatology/dentistry/surgery, and health/nursing/medicine fields, and research frontiers cover the fields of molecular/biology/immunology, dentistry/dermatology/surgery, and medicine/medical/clinical. Furthermore, the green curve (Figure 3) serves as a reminder that basic science can guide clinical application.

Hotspots and Frontiers

According to the analysis of keywords and co-cited references, the research on vitiligo can be briefly divided into four aspects: (1) clinical characteristics, (2) epidemiology and genetics, (3) pathogenesis, and (4) treatment. Table 2 lists the hotspots and frontiers of the above four research orientations.

In the aspects of clinical characteristics, cluster #8 "quality of life" and cluster #13 "depression" are considered hotspots in vitiligo research. Vitiligo patients experience discrimination and stigma due to their appearance, which leads to a decline in self-esteem and avoidance or restriction of social interactions [16]. Consequently, the prevalence of psychosocial and psychiatric morbidity in vitiligo individuals is significantly higher than healthy individuals [17-19]. Over the past two decades, research interest in the psychology and quality of life of vitiligo patients has increased greatly. And several assessment instruments were used to investigate the quality of life of vitiligo patients. Dermatology Life Quality Index, a practical and proven questionnaire designed to assess the impact of skin diseases on quality of life [20], is widely applied in the field of vitiligo. In recent years, more specific assessment tools have been developed for patients with vitiligo, for example, VitiQoL and Vitiligo Impact Patient scale [21-22]. Despite their development, these tools are not widely employed in clinical practice. Therefore, it becomes crucial to utilize them for further validation, which is a recent keyword, indicating that validation is also a significant aspect of the current hotspots and frontiers. In addition to the above assessment tools for quality of life, multiple scores and indexes evaluating disease activity, severity, or area of lesion of vitiligo have been designed [23-25]. However, these tools still require validation in clinical research.

Epidemiology and genetics are also popular research areas. Over the past two decades, researchers have carried out extensive epidemiological studies on vitiligo. Cluster #11 "prevalence" reveals this academic hotspot. "comorbidity" is a recent keyword. Numerous studies have revealed the common occurrence of vitiligo alongside other disorders, especially autoimmune diseases [26]. Furthermore, the association between vitiligo and metabolic syndrome has recently gained academic attention. Cluster #1 "association" is another hotspot, with a number of genome-wide association studies revealing various vitiligo susceptibility loci. Among them are genes encoding proteins involved in immunoregulation, apoptosis, and melanocyte function [27]. Additionally, the identification of shared susceptibility genes between vitiligo and other autoimmune diseases helps to explain the epidemiological associations observed among them. Moreover, cluster #15 "immunotherapy" and the recent keyword "nivolumab" represent another hotspot. Immunotherapy drugs, including nivolumab, can be used to treat melanoma. Interestingly, vitiligo, which is considered as a clinically visible immune-related adverse event, is associated with clinical benefit [28]. It is noteworthy that treatments for melanoma and vitiligo seem to be at opposite ends of the spectrum.

Therefore, gaining a profound and better understanding of the underlying association in terms of the mechanisms of these two diseases will greatly benefit clinical treatments for both.

The study of the pathogenesis of vitiligo is a significant and ongoing topic in the field. Current mainstream studies on the pathogenesis mainly focus on oxidative stress, intrinsic abnormalities of melanocytes, and T cell-mediated autoimmune attack on melanocytes. Oxidative stress plays a crucial role as an initiating factor [29]. Melanocytes, due to their inherent defects, are unable to regulate both the endogenous oxidative stress of melanin production and exogenous oxidative stress of the external environment, leading to damage. Additionally, oxidative stress triggers a signaling cascade by releasing DAMPs, exosomes, IL-1β, IL-18, and other molecules, which then activate the innate immune response [30-31]. The innate immune system then triggers the adaptive immune system by activating dendritic cells, promoting targeted autoimmune destruction of melanocytes. As shown in Figure 5B, early studies on the pathogenesis of vitiligo primarily focused on cluster #5 "melanocyte" and #10 "hydrogen peroxide". Later, clusters #14 "dopamine pathway", #3 "IL-17," and #0 "oxidative stress" gained attention. Furthermore, the unfolded protein response (UPR), which has received increasing attention, is a potential hotspot. UPR is a cellular restoration that occurs in response to inappropriate protein folding caused by oxidative stress-induced dysfunction of the endoplasmic reticulum [32]. The activation of UPR in stressed melanocytes and keratinocytes can regulate the release of chemokines, mediate recruitment of CD8+T cells to skin in vitiligo and trigger an immune attack on melanocytes [33]. Additionally, "migration" has become a prominent topic, with strong citations observed from 2018 to 2023. The migration of melanocytes to the lesional area is an important repigmentation process. Recent studies have concentrated on the mechanisms and patterns of repigmentation during treatment and have examined the involvement of melanocyte stem cells in this process [34-35]. Moreover, "biomarkers" is a recent keyword highlighted in the red cluster, indicating a growing interest in identifying potential biomarkers for objectively diagnosing and assessing the activity and the severity of vitiligo and evaluating therapeutic response. Chemokine C-X-C motif ligand 10 (CXCL10) is a trending biomarker which predicts lesional leukocytic infiltration and vitiligo treatment response and outcome [36].

Over the past two decades, researchers have extensively explored treatment methods of vitiligo so as to prevent progression, stabilize pigmentation, and promote repigmentation. Currently, the available treatments primarily consist of local and systemic immunosuppressants, phototherapy, calcineurin inhibitors, and surgical techniques. Among them, phototherapy is a more extensive approach to treat vitiligo. PUVA photochemotherapy was an early hotspot and was the first phototherapy for vitiligo. However, due to its side effects and increased risk of skin cancer, it has now been largely replaced by NB-UVB [37-38]. NB-UVB and 308-nm excimer laser can induce melanocyte proliferation and migration and play an immunosuppressive role, and they have been widely used in clinical therapy [39]. Fractional carbon dioxide laser is a novel hotspot in recent years. A series of publications have reported its effectiveness as an add-on to conventional treatments [40]. After deep and extensive exploration of pathogenesis, innovative drugs will be developed in clinical practice to specifically target the treatment of vitiligo. One promising avenue for this is the use of Janus kinase (JAK) inhibitors, which can contribute to repigmentation by disrupting IFN-γ signaling, a significant factor in vitiligo pathogenesis. This emerging field shows great potential for the future. Additionally, there is a growing interest in the use of platelet-rich plasma and 5-fluorouracil for treating vitiligo [41-42]. However, further studies are required to determine their safety and efficacy.

Conclusion

In this bibliometric study, we reviewed publications related to vitiligo published between 2002 and 2023, visualized the outputs, distribution, and collaboration of research forces, and identified significant contributors to the field. Additionally, we explored the hotspots and frontiers of vitiligo from the aspects of clinical characteristics, epidemiology and genetics, pathogenesis, and treatment to assist researchers in better grasping the development trends.

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