

REVIEW



Anti-inflammatory effects of immunotherapy in clinical treatment and its potential mechanism in alleviating sleeping disorders: A systematic bibliometric study

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ABSTRACT

Sleeping disorders negatively affect cancer patient management, quality of life, and recovery. Immunotherapy, a rising cancer treatment, shows potential to improve sleep quality by reducing inflammation. This study analyzed 255 publications (2000-2024) from the Web of Science Core Collection using bibliometric methods. The US and China dominate research output, with The Mayo Clinic as a key contributor. Core topics are "immunotherapy," "quality of life," and "antibodies." Emerging keywords like "cancer," "encephalitis," and "depression" highlight a shift toward clinical psychology in treating tumors and rare diseases. It is noteworthy that with the rapid expansion of immunotherapy in cancer treatment, clinical trials have shown that it can improve sleep quality in cancer patients by reducing inflammation. As its application in cancer treatment expands, immunotherapy's potential for treating sleep disorders is promising. Future development is expected to improve sleep quality and address clinical issues, offering broad prospects for patient outcomes.

ARTICLE HISTORY

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KEYWORDS

Immunotherapy; sleeping disorders: bibliometrics: cancer; survival

Introduction

Sleeping disorders are a growing health problem¹ in today's fast-paced societe that not only affect an individual's mental state and quality of life but are also strongly associated with multiple chronic medical conditions,² mental illness,^{3,4} and cancer.⁵ The etiological factors of sleeping disorders are diverse. Circadian rhythm disruption, psychological disorders, endocrine imbalances, elevated inflammatory factors, and airway obstruction can all lead to sleeping disorders.⁶ As an emerging and promising treatment method, immunotherapy is gradually showing its unique advantages in the treatment of a variety of diseases. Modulating host immune responses through immune system manipulation constitutes a cuttingedge therapeutic approach for disease management. Immune checkpoint inhibitors 6 (ICIs),7 chimeric antigen receptor T-cell (CAR-T cells),8 dendritic cell vaccines,9,10 and cytokine therapies, 11 among others, have made great progress in oncology in recent years. 12 Drugs such as pembrolizumab and nivolumab, which block the PD-1/PD-L1 and CTLA-4 pathways, have excellent efficacy against cancers such as melanoma, non-small-cell lung cancer (NSCLC), and renal cell cancer, as well as hematologic malignancies such as leukemia and lymphoma.¹³ Regulation of immune signaling by glucagon-like peptide-1 receptor agonists prevents the production

and release of inflammatory cytokines such as tumor necrosis factor- α (TNF- α) and interleukin-6 (IL-6). They also promote the activation of anti-inflammatory mechanisms, such as the AMP-activated protein kinase (AMPK) pathway, which helps suppress inflammation. It also has potential for cancer treatment¹⁴ However, the interplay between immunotherapy and sleeping disorders, along with its underlying mechanisms, remains partially elucidated and warrants further exploration. Hence, the objective of this study is to conduct a comprehensive analysis of the extant literature regarding the interplay between immunotherapy and sleeping disorders. This article aims to conduct a comprehensive review of the extant research landscape, pivotal thematic domains, and prospective research trajectories through bibliometric methods, with a particular focus on elucidating the underlying mechanisms linking immunotherapy and sleeping disorders.

In recent years, with the global attention to the study of sleeping disorders, a significant escalation in the volume of scholarly publications pertaining to the subject has been observed. An examination of the publication counts across several databases reveals a steady advancement in sleeping disorder research, which spans a broad spectrum of topics, with a particular emphasis on epidemiological investigations, pathophysiology, diagnosis, and treatment methods. Among

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them, the research on the development of new drugs for sleeping disorders, the exploration of non-pharmacological treatment methods, and cognitive behavioral therapy are particularly active. It is noteworthy to emphasize that immunotherapy, increasingly adopted in clinical settings, is garnering attention for its potential application in addressing sleeping disorders.

As a novel area at the crossroads of medical and biological sciences, the nexus between immunotherapy and sleeping disorders is garnering escalating research interest, with a marked annual growth in the volume of pertinent scholarly discourse. This represents a significant challenge for investigators who are novices in this domain, especially for nonprofessionals who have a strong interest in this topic, to quickly grasp and summarize the knowledge system in this field in a short time. Characterized by quantitative analysis, objectivity, revealing knowledge structures, predicting research trends, and crossdisciplinary applications, bibliometrics serves as an analytical framework that integrates mathematical and statistical techniques to assess academic literature within a specific domain, covering both qualitative and quantitative dimensions of analysis, and is capable of forecasting trends in the field and elucidating collaborative networks among scholars. 15,16 It can forecast trends in the field and elucidate the collaborative networks among scholars. It is worth noting that although the relationship between immunotherapy and sleeping disorders has been widely discussed in the medical community, no systematic bibliometric study has been published in this field. This investigation represents the inaugural endeavor to address this research void by amalgamating bibliometric analysis with knowledge mapping methodologies, we can comprehensively and objectively describes the immune therapy and the relationship between sleeping disorder the evolution of this field, the current research hot spot, the development trend of the future as well as the newly emerging issues are discussed.

Materials and methods

Data sources

Since its inception in 1985, Web of Science Core Collection (WoSCC) has played a pivotal role in the field of scientific research due to its excellent ability to integrate academic information. The science citation index database set extension (SCIE), social science citation index (SSCI), and the arts and humanities citation index (A&HCI), and other core resources into an organic whole, research workers for the global platform provide a comprehensive, in-depth academic exploration. The dual core strengths of WoSCC, namely reference tracking and citation reporting, in conjunction with a stringent selection process adhering to Bradford's law of bibliometrics, are pivotal in shaping the landscape of scholarly communication, 17 are key differentiating factors that set WOSCC apart from other academic databases. The reference tracking function ensures the continuity and traceability of academic research, enables researchers to systematically trace the evolution of academic ideas, and provides a solid foundation for scientific research innovation. Citation reports provide a scientific basis for evaluating the impact of academic achievements through

quantitative analysis, which helps researchers to clarify their position and contribution in the academic field. In view of the nature of the database being updated daily, to ensure the uniformity and comparability of the search outcomes and to mitigate the potential influence of bias, a concurrent search strategy was employed on a single day for all inquiries.

Our search formula is "(TS=(Sleep disorder OR Insomnia OR hyposomnia OR Narcolepsy OR Somnolence OR sleep apnea OR sleep disturbance OR" sleep quality OR Sleep deprivation OR)) AND TS=("immunotherapy" OR "immunotherapies" OR "immunotherapeutic" OR OR "immune therapy" OR "immunomodulator" OR "PD-L1 inhibitors" OR "PD-1 inhibitors" OR "CTLA-4 inhibitors" OR "cellular immunotherapy" OR "immune checkpoint inhibitor" OR "nivolumab" OR "pembrolizumab" OR "lambrolizumab" OR "atezolizumab" OR "avelumab" OR "durvalumab" OR "ipilimumab" OR "pidilizumab" OR "cemiplimab" OR "durvalumab" OR "ipilimumab" OR "camrelizumab" OR "Sintilimab" OR "Toripalimab" OR "Tislelizumab" OR "Cadonilimab" OR "Zimberelimab" OR "SlurryMab" OR "Penpulimab" OR "Envafolimab" OR "Adebrelimab" OR "Sugemalimab") retrieved a total of 357 papers, and 257 papers remained after excluding reviews and other papers that did not meet the requirements, and two papers that were not highly relevant to the topic were excluded through re-screening, and 255 papers were finally left. The final 255 remaining literatures were used as the total database for analysis (Figure 1).

Methods and software

V4.3.1 (R) language bibliometrix package was used for data operation按, statistical visualization and analysis of the literature metrology, complete the construction of a national/regional level scientific output figure, keyword cloud image, thematic map, theme trend chart. VOSviewer 1.6.19 was used for literature visualization analysis to display the clustering view, label view, and density view of literature data, and to construct the author cooperation network map and keyword co-occurrence map. Citespace6.3.1 was used for the drawing and analysis of keyword time map. Employing V4.3.1 (R), VOSviewer 1.6.19, and Citespace 6.3.1, we analyzed publication counts, geographical origins, institutional contributions, journal sources, authorship, citation frequencies, and keyword distributions, followed by visual mapping to discern and detail their distinctive attributes.

Ethical clearance

The study does not require any ethical clearance

Results

Analysis of annual number of publications

A total of 255 articles related to immunotherapy and sleeping disorders were retrieved from the Web of Science Core Collection (WoSCC). In Figure 2, the year with the lowest number of publications was 2007, with 0 articles, while the highest number of publications occurred in 2022, with 34

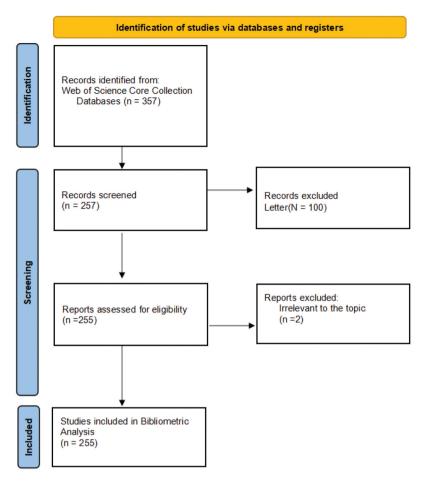


Figure 1. Flow chart about the search strategy from papers related to immunotherapy and sleep disorders.

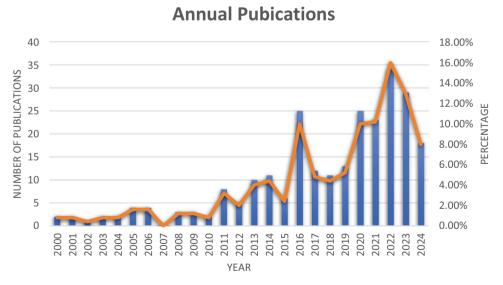


Figure 2. Number of publications with time from 2000 to 2024. (The blue bar chart represents the number of publications each year, while the brown line chart indicates the proportion of annual publications relative to the total number).

articles. The average annual publication rate was ten articles. As shown in the figure, between 2000 and 2015, the number of publications fluctuated slightly and remained very low, indicating that the field had not yet attracted

significant attention from the academic community. However, from 2016 to 2024, there was a rapid increase in the number of publications related to this field. In summary, although specific trends may vary due to

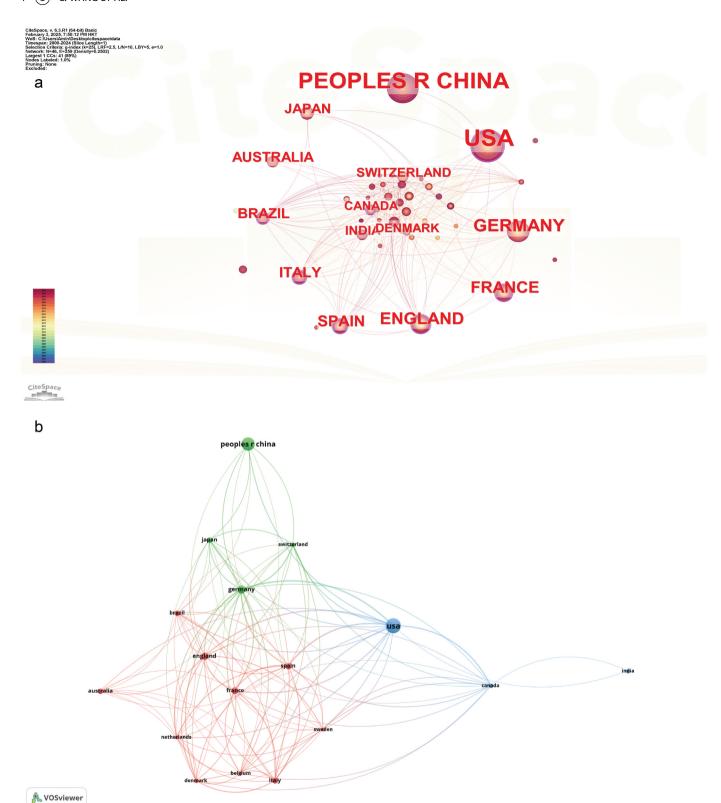


Figure 3. A visual map of countries and institutions associated with immunotherapy and sleep disorders. (a) CiteSpace network analysis map of countries/regions. (b) VOSviewer country collaboration analysis map.

different data sources and statistical methods, the increase in publication volume suggests that research on the interplay between immunotherapy and sleeping disorders has made significant progress.

Country/region analysis

The Citespace country/region network analysis chart is used to analyze the scientific output of different countries and explore the distribution of scientific research results. The VOSviewer country collaboration analysis chart is used to visually display the cooperation between countries and the volume of publications.

In Figure 3a, the size of the nodes represents the number of publications from a country, with larger nodes indicating a higher number of published papers. The purple area within the nodes indicates the strength of centrality, with higher values suggesting better collaborative relationships. The ranking of publication volumes from highest to lowest is as follows: the United States leads with 82 articles (32.16%), followed by China with 67 articles (26.27%), Germany with 25 articles (9.80%), the United Kingdom with 20 articles (7.84%),

France with 18 articles (7.06%), Spain with 15 articles (5.59%), Italy with 13 articles (5.10%), Australia with 12 articles (4.70%), Brazil with 12 articles (4.70%), and Japan with 11 articles (4.31%). A betweenness centrality (BC) value greater than 0.1 indicates a key node. Corresponding to Figure 3b, although Canada does not have a high number of publications, it still occupies a central position in international cooperation with a centrality of 0.23. The United States and Germany are countries with both high publication volumes and high centrality, while China, despite its high publication volume, has a relatively low centrality.

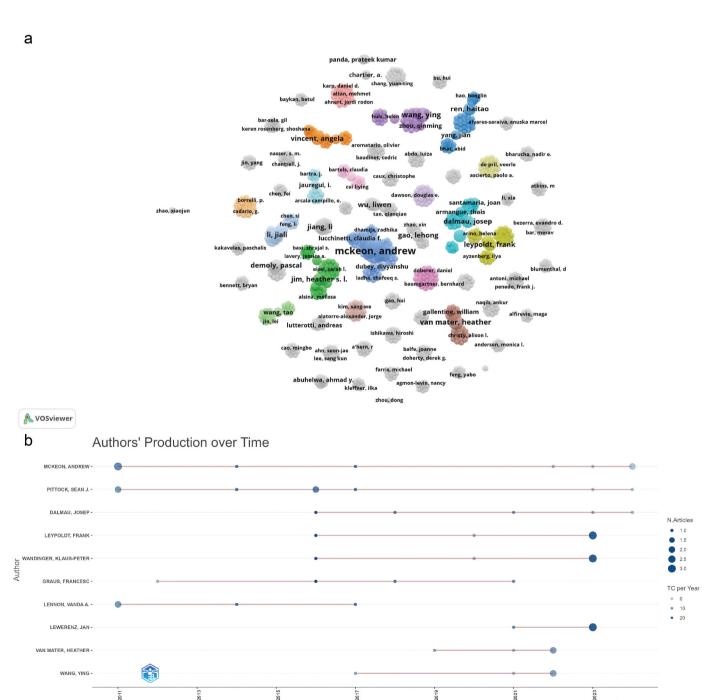


Figure 4. A visual map of authors associated with sleep disorders and immunotherapy. (a) Visualization analysis of author collaborations. (b) Author's publication volume-time.

Institutions and authors

When we deeply discuss the author's contribution and scientific research productivity in the academic field, visualization analysis of author collaborations (Figure 4a) and the author's publication volume-time graph (Figure 4b) can be used as our visualization tools, which together reveal the rich academic dynamics of the author. Visualization analysis of author collaborations intuitively shows the differences in the number of papers published by different authors at a specific time. Among them, MCKEON, ANDREW, PITTOCK, SEAN J. The significant performance of DALMAU, JOSEP, and other scholars highlights their deep accumulation and high activity in this field. This distribution not only reflects the efforts and achievements of individual research but also reflects the imbalance of research power within the field. At the same time, combined with the analysis of the time dimension of scientific research output by the author's publication volume - time graph, we found that from 2011 to 2023, the number of papers published per Year (TC per Year) of many scholars, including LEYPOLDT and FRANK, showed a fluctuating upward trend. This not only reflects the sustainability and accumulation of academic research, but also reveals that the research environment plays a positive role in promoting the growth of scholars. Although each scholar's output path has its own characteristics, the overall steady growth of scientific research contribution reflects the continuous improvement of scientific research productivity in the academic field. However, the author partnership map shows that among global authors, we find that the cooperative relationship between authors from different countries and different institutions is weak.

When discussing the current trend of collaboration and influence distribution in the field of academic research, one aspect that cannot be ignored is the volume and correlation of publications between institutions. This paper describes the number of publications and the academic cooperation network of different academic institutions in the field of research by using the Top ten published Affiliations ranked by H-index (Figure 5a) and Institutional cooperation relationship graph (Figure 5b).

On the whole, two graphs clearly shows the close cooperation and interrelation of many well-known institutions in a certain research field. These institutions include, but are not limited to, MAYO CLINIC, UNIVERSITY OF BARCELONA, DUKE UNIVERSITY, etc., each of which has made academic contributions and research achievements in the field. MAYO CLINIC leads the way as the highest publishing institution with 40 papers. Far more than any other institution. It is worth noting that the cooperative relationships of these institutions are not equal, but rarely related, which reveals the imbalance and hierarchical structure of academic cooperation. These disparities could be significantly associated with myriad factors, including research capacity, resource input, research direction, and the degree of international cooperation of institutions. In the future research, we ought to enhance focus on inter-institutional exchange and collaborative efforts, promote knowledge sharing and resource integration, and jointly promote the progress and development of academic research.

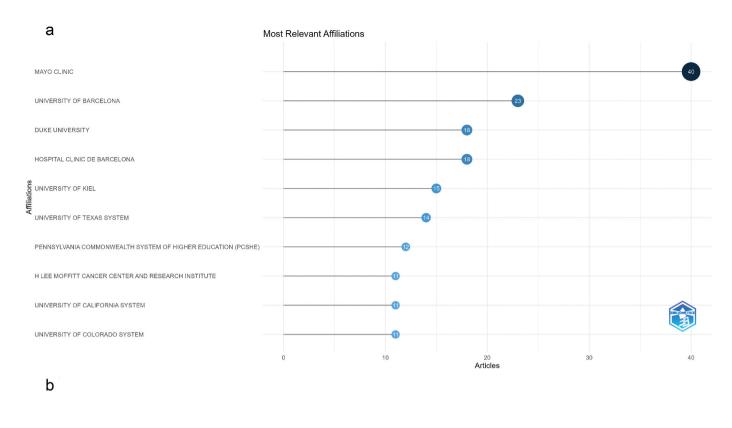
Keywords

Keywords, as the concise content of the article, directly reflect the main idea and core content of the research. In this study, we adopted a comprehensive strategy to merge various variants of the same keyword (covering abbreviations, hyphen forms, etc.), and used bibliometrix package to make Wordcloud (Figure 6a) to visually display the word frequency and importance of the top 50 keywords with weight. We use VOSviewer to create Co-occurrence network map of keywords (Figure 6b) in order to show the relationship and development between each keyword. Among the 1428 keywords, the most frequently used keywords were immunotherapy (n = 39), quality of life (n = 30), and antibodies (n = 29), while sleep (n = 14) was the only keyword related to sleeping disorders

Trends and key issues in the field of immunotherapy for sleeping disorders were analyzed based on years. In the limited number of words, 27 hot topics were extracted for "2000-2023" (Figure 6c,e). In the figure, the size of the circle directly reflects the frequency of keywords. High-frequency keywords are presented in larger circles, and vice versa, they are represented in smaller circles. In the evolution of the key themes, we found that the keywords under this theme were mentioned more and more after 2013. "Immunotherapy," "quality of life," and "antibodies" mentioned above were the most popular in the period from 2016 to 2018, while "encephalitis" and "diagnosis" were prevalent keywords in recent years. In order to comprehensively track the evolution of these keywords, we used CiteSpace to construct the labels clustering of co-cited literature based on LLR algorithm (Figure 6d), which not only clustered keywords, but also integrated the timeline dimension. This innovative approach enables us to clearly observe the evolution trajectory of each topic in the field of the effect of immunotherapy on sleeping disorders over time, and to quickly grasp the latest progress and frontier trends in this field. It vividly shows the occurrence time sequence of each keyword through the tree ring structure of nodes. Larger tree rings indicate earlier appearance, and smaller rings indicate more recent appearance, thus depicting a detailed evolutionary picture of the application of immunotherapy in the field of sleeping disorders.

Citations and journals

Citation analysis, a pivotal instrument for gauging the academic impact of scholarly outputs, not only exposes the extensive dissemination and acknowledgment of research findings, but also provides a valuable perspective for identifying current research hotspots and trends by digging deeply into highly cited articles (Figure 7a,b). We deeply observed the academic impact of articles in different years and their interrelationships. Between 2013 and 2017, the publication and citation activities of the literature were particularly active, among which the literatures of Graus F (2016) and Bastiaansen AEM (2017) highlighted their key role and influence in the field due to their large point size and rich connection lines. Indicating their role as Bridges and links in academic discussion and research development. It is particularly noteworthy that Irani SR (2012, 2013), although not the most cited, is closely linked to other literatures, demonstrating their importance in



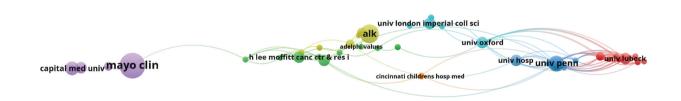




Figure 5. Visualization of affiliations. (a) Top ten published affiliations ranked by H-index, (b) Institutional cooperation relationship graph.

building academic dialog and promoting knowledge exchange. In addition, the citation explosive publication from 2014 to 2017 further emphasizes the significant influence of the literature in this period. In particular, the literature of Grau F (2016) has the highest citation intensity between 2019 and 2021, which may indicate its far-reaching influence in the field of

neurology and its central position in the academic community. These data not only provide us with a snapshot of important literature and research trends within the field of neurology, but also help us understand the focus of academic attention and its evolution over a given time period. Through an in-depth analysis of these literatures, we can better grasp the context

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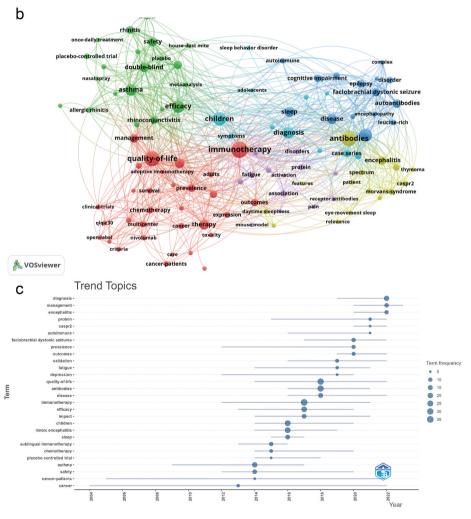


Figure 6. A visualization of the keywords. (a) Wordcloud. (b) Co-occurrence network map of keywords. (c) Trend topic.

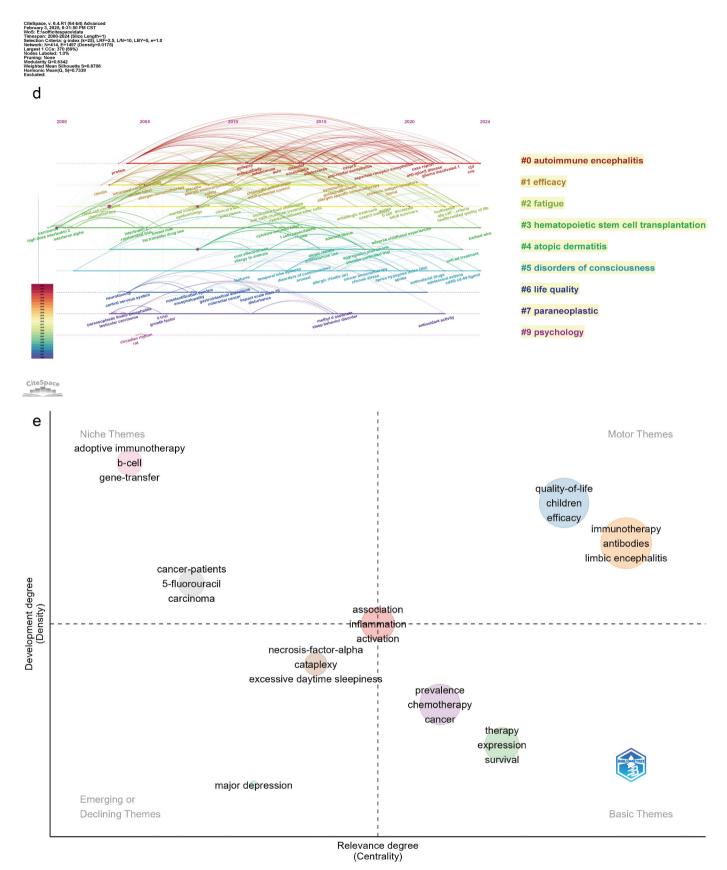
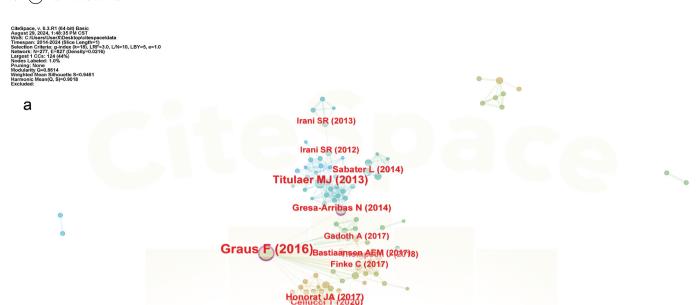


Figure 6. d) Labels clustering of co-cited literature based on LLR algorithm. (e) Strategic coordinate map of themes.



b Top 20 References with the Strongest Citation Bursts

References	Year Stre	ength Begin End 2014 - 2024
Titulaer MJ, 2013, LANCET NEUROL, V12, P157, DOI 10.1016/S1474-4422(12)70310-1, DOI	2013	4.02 2014 2017
Adams C, 2011, ARCH NEUROL-CHICAGO, V68, P521, DOI 10.1001/archneurol.2011.56, DOI	2011	1.37 2014 2016
Prüss H, 2012, ANN NEUROL, V72, P902, DOI 10.1002/ana.23689, <u>DOI</u>	2012	2.11 2015 2016
Armangue T, 2014, ANN NEUROL, V75, P317, DOI 10.1002/ana.24083, DOI	2014	1.39 2015 2017
Sabater L, 2014, LANCET NEUROL, V13, P575, DOI 10.1016/S1474-4422(14)70051-1, DOI	2014	3.11 2016 2017
Irani SR, 2012, ANN NEUROL, V72, P241, DOI 10.1002/ana.23577, DOI	2012	2.58 2016 2017
Irani SR, 2013, BRAIN, V136, P3151, DOI 10.1093/brain/awt212, <u>DOI</u>	2013	2.32 2016 2018
Simabukuro MM, 2015, NEUROL-NEUROIMMUNOL, V2, P0, DOI 10.1212/NXI.00000000000136, DO	2015	2.06 2016 2017
Högl B, 2015, LANCET, V385, P1590, DOI 10.1016/S0140-6736(15)60445-7, DOI	2015	2.06 2016 2017
Graus F, 2016, LANCET NEUROL, V15, P391, DOI 10.1016/S1474-4422(15)00401-9, DOI	2016	6.25 2019 2021
Honorat JA, 2017, NEUROL-NEUROIMMUNOL, V4, P0, DOI 10.1212/NXI.000000000000385, DOI	2017	1.93 2020 2022
van Sonderen A, 2016, NEUROLOGY, V87, P521, DOI 10.1212/WNL.000000000002917, DOI	2016	1.91 2020 2021
Gaig C, 2017, NEUROLOGY, V88, P1736, DOI 10.1212/WNL.00000000003887, DOI	2017	2.61 2021 2022
Bastiaansen AEM, 2017, CURR OPIN NEUROL, V30, P302, DOI 10.1097/WCO.000000000000444, DOI	2017	2.17 2021 2022
Finke C, 2017, JAMA NEUROL, V74, P50, DOI 10.1001/jamaneurol.2016.4226, DOI	2017	2.17 2021 2022
Thompson J, 2018, BRAIN, V141, P348, DOI 10.1093/brain/awx323, DOI	2018	2.17 2021 2022
Montagna M, 2018, FRONT NEUROL, V9, P0, DOI 10.3389/fneur.2018.00329, DOI	2018	1.73 2021 2022
Cellucci T, 2020, NEUROL-NEUROIMMUNOL, V7, P0, DOI 10.1212/NXI.000000000000663, DOI	2020	2.75 2022 2024
Cabezudo-García P, 2020, ACTA NEUROL SCAND, V141, P263, DOI 10.1111/ane.13207, DOI	2020	1.48 2022 2024
Chung HY, 2019, MEDICINE, V98, P0, DOI 10.1097/MD.000000000015706, DOI	2019	1.48 2022 2024

Figure 7. Citations analysis. (a) The co-citation network of literature. (b) Top 25 most cited references.

of academic research, predict possible future research directions, and provide valuable references and inspirations for the academic community.

Top ten published journals ranked by H-index (Figure 8) provides an overview of the amount of literature in the most relevant journals in the field. "Frontiers in Neurology," "Journal of Neuroimmunology," "Neurology," and "BMC

Neurology" highlight their leadership. In neuroscience research, the substantial publication output is notable, particularly as the majority of these publications are associated with neurology-focused journals. Frontiers in Neurology is a leading open access journal, and its rich literature volume reflects the important role of open access publishing model in promoting academic communication. The high number of

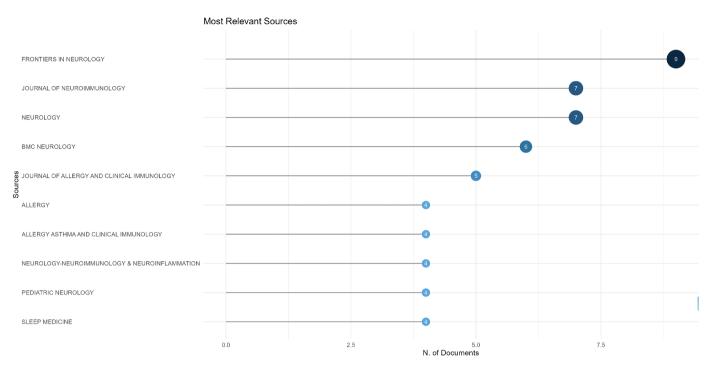


Figure 8. Top ten journals ranked by the number of publications.

articles in Journal of Neuroimmunology highlights neuroimmunology as a hot field of current research. In addition, "Allergy," "Allergy, Asthma & Clinical Immunology, Neurology-NeuroImmunology & Neuroinflammation, Pediatric Neurology, and Sleep Medicine, and other journals also published at least 20 number of articles in their specific fields, indicating that this field is more inclined to explore the neuroendocrine system.

Discussion

General information

With the continuous progress of academic research, bibliometrics has become increasingly widely used in academia. It has become an important tool 18 to appraise scientific publications, monitor research trajectories, and assess the advancement in specific scholarly domains. Previous studies have revealed that immunotherapy holds potential value in improving sleeping disorders, particularly in cancer treatment, where its anti-inflammatory effects may positively alleviate sleep issues in patients. By reviewing relevant literature from 2000 to 2024, this study aims to provide an overview of the current state of the field, including research hotspots, leading authors, institutions, countries and so on.

Since the first article on the effect of immunotherapy on sleeping disorders was published in 2000, there has been a rising trend in the volume of pertinent literature sleeping disorders. Prior to 2010, the annual publication count did not exceed five, reflecting a relative lack of attention to the field. In 2011, the annual number of articles doubled for the first time. In 2016, more and more treatments for allergic immune diseases and emerging antibody therapies caused an exponential rise in the volume of scholarly publications. At the same time,

immunotherapy for cancer and some rare diseases and sleeping disorders began to be gradually linked. ^{19,20} Finally, the number of publications peaked in 2022, and more attention was paid to the relationship between cancer, immunotherapy, and sleeping disorders.

In the analysis of countries and institutions, The United States leads in both publication output and advancement pace within this domain. The top ten publishing institutions are mainly from the United States, and the number of citations is greater than the sum of other countries, indicating the authority and centrality of the United States in this topic, and serving as a bridge for communication between various countries in this topic. Mayo Clinic has established an unquestionable authority with its number of publications and citations ranking first in this field. Its research is not only comprehensive in breadth and coverage, but also at the forefront of the industry in depth, which has significantly contributed to the advancement and evolution of this domain.

In analyzing the collaborative relationships, citation indices, and publication venues of authors like MCKEON, ANDREW, and PITTOCK, it is evident that their prolific publication records reflect significant scholarly contributions and active engagement in the field. However, this also underscores an uneven distribution of research influence of publications, but also revealed the imbalance of research power in the field. From the perspective of time dimension, the number of papers published by scholars generally showed a fluctuating upward trend, reflecting the continuous accumulation of academic research and the positive help of the research environment. Although each scholar's research path is unique, the steady growth of overall research productivity is obvious. However, the author collaboration graph reveals a problem that cannot be ignored: worldwide, author collaboration between different countries and institutions is relatively



weak. Therefore, international collaboration is needed to deepen research in the future.

Through the in-depth extraction and detailed analysis of keywords, we can clearly gain insight into the core research hotspots and continuous focus of attention on the effect of immunotherapy on sleeping disorders. In this field, in addition to the keywords used for retrieval, the key word "quality of life" appeared with a high frequency, highlighting its position as the focus of research, followed by "antibody," "children," "encephalitis," "asthma," etc. These terms together constitute the basic content and object of CAR-T cell therapy research. A further dig into the relevant literature and reference materials, it is not difficult to find that the research focus of the effect of immunotherapy on sleeping disorders is highly focused on the fields of "cancer" and "immunotherapy" and "mental related," which coincides with the research results of the highimpact papers in the field, and further verifies the accuracy and representability of the research trends revealed by these keywords.

The special "four-quadrant map" and "thematic trend map" revealed some interesting changes. In addition to the common keywords under this topic, we also found the key word "depression," which belongs to the category of clinical psychology with sleeping disorders. It is well known that depression and sleeping disorders often have a concomitant relationship. 21 The inflammatory hypothesis, 22,23 hormonal regulation changes,²⁴ and genetic relationship^{25,26} have revealed an inseparable link between the two. The interplay among immunotherapy, sleeping disorders, and depression may constitute an emerging research frontier.

The analysis and mining of high-frequency keywords is not only a key tool to understand the current research dynamics and trends, but also an important means to grasp the core concepts of the field, identify research hotspots, and provide direction for scientific research exploration.

Knowledge base

Immunotherapy is an emerging treatment method in recent years, which plays a significant role in the treatment of a variety of diseases, especially cancer.^{27–29} In terms of classification, it is mainly based on immune checkpoint inhibitors (ICI), chimeric antigen receptor T cells (CAR-T cells), dendritic cell vaccines and cytokine therapy. Immune checkpoint inhibitor therapy is currently the most widely used therapy in clinical practice. In the treatment of cancer, its principle is to prevent cancer cells from escaping by inhibiting immune checkpoint proteins (such as PD-1, etc.) of immune cells.³⁰ PD-1 is expressed on the surface of T cells and mainly acts in the periphery,³¹ while PD-L1, as a ligand of PD-1, is expressed on a variety of cells, including tumor cells.³² When PD-1 binds to PD-L1, it transmits an inhibitory signal that inhibits T-cell receptor-mediated suppression of lymphocyte proliferation and cytokine secretion.³³ Immune checkpoint inhibitors (such as anti-PD-1 or anti-PD-L1 antibodies) can block this binding. PD-1 inhibitors commonly used in clinical practice include nivolumab, pembrolizumab, pyridinizumab, AMP-224 and AMP-514, nivolumab, etc. PD-L1 inhibitors include atezolizumab, durvalumab, and nivolumab. These drugs can

relieve the inhibitory effect of T cells, restore their anti-tumor activity, and have the advantage of stronger resistance than conventional anti-tumor drugs. 34-36

Sleeping disorders are a global public health problem, which is closely related to chronic diseases such as cardiovascular diseases, ³⁷ malignant tumors, cerebrovascular diseases, diabetes, sepsis, and hypertension. Sleeping disorders have a high incidence in all races and all ages around the world. Sleep is closely related to the human immune system, and normal and regular sleep is essential for the immune system. During sleep, the body will repair and adjust itself, releasing cytokines and other immune-related substances. These substances play an important role in resisting the invasion of pathogens and regulating the balance of the immune system, but they may also be related to the increase of inflammatory factors in pathological states.³⁸ Adequate sleep can enhance the immune response, and the immune response of most immune cells peaks at night,³⁹ which helps the body fight off infections and diseases. Sleeping disorders or reduced sleep duration may lead to a series of problems in the body's immune system, and sleeping disorders will directly affect the normal operation of the immune system. Sleeping disorders can cause stress responses in the body and affect the hormone regulatory axis in the body, such as the hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous system (SNS),⁴⁰ resulting in imbalance of hormone levels in the body, such as increased secretion of stress hormones such as cortisol, 41 which may inhibit the activity of the immune system and weaken the body's resistance to diseases. Long-term lack of sleep or poor sleep quality will disrupt the immune regulatory mechanism, resulting in the body's inability to effectively produce and regulate immune substances, thereby reducing the function of the immune system.

At present, the data on the effect of immunotherapy on sleeping disorders mainly come from clinical observation and detection in cancer treatment. A 2023 experiment comparing chemotherapy and immunotherapy in cancer NSCLC patients shows that immunotherapy drugs themselves do not cause sleeping disorders, and can quickly alleviate sleeping disorders through the therapeutic effect.⁴² Sleeping disorders are associated with increases in inflammatory markers, including interleukin (IL) -6 and C-reactive protein (CRP), as well as serum amyloid-α, tumor necrosis factor-α, and granulocytemacrophage colony-stimulating factor. 43,44 In the initial stage of treatment, immunotherapy blocks the suppression of the immune system and temporarily exacerbates inflammation in the body. However, with the positive response of the disease, the secretion of inflammatory factors is significantly reduced, which is not only a reflection of the self-regulation of the immune system, but also a positive signal of the impact on sleeping disorders. 45,46 Moreover, patients with higher PD-L1 status have faster response and longer response time, and the symptoms of sleeping disorders can be relieved faster. 47,48 For sleeping disorders caused by more common diseases, the effect of immunotherapy on it is still far from being investigated. 49,50

Limitations

Although tools such as CiteSpace and VOSviewer play an important role in bibliometric analysis, they cannot completely

replace a comprehensive and systematic retrieval process, and it is difficult to directly integrate data from multiple databases for comprehensive analysis. Secondly, although this study has retrieved and downloaded all relevant data from WoSCC (assuming a comprehensive science citation database), it is still possible that important publications that are not included in the WOSCC database have been missed, and the cited literature only contains English publications, which introduces language bias, which may affect the comprehensiveness of the research results. In addition, bibliometric methods focus on quantitative analysis, such as the number of publications and the frequency of citations, but it is often difficult to comprehensively assess the quality of publications. Therefore, there is a risk that high-quality studies are obscured by low-quality studies. However, we believe that these limitations, while present, are unlikely to materially bias the overall understanding of research trends in the field of the effects of immunotherapy on sleeping disorders. In summary, considering WoSCC is one of the widely used and recognized authoritative databases for bibliometric analysis, visual analysis based on WOSCC data can still effectively assist researchers to fully understand the research hotspots, evolution and future development trends of immunotherapy on sleeping disorders, and provide valuable reference and enlightenment for further research in related fields.

Conclusion

This study explored the association between immunotherapy and sleeping disorders through bibliometric methods, and discerned the evolutionary trends in this domain post-2000. The study pointed out that although there was little attention in the early days, the potential positive effects of immunotherapy on sleeping disorders have gradually received attention in recent years. In the realms of oncology and rare diseases, immunotherapy's application not only circumvents the induction of sleeping disorders but also manifests a propensity for enhancing sleep quality in patients, conferring a significant therapeutic advantage, particularly in the context of cancer chemotherapy. This finding may be related to the reduction of inflammatory markers in the body by immunotherapy, which clinically regulates various clinical psychological symptoms of patients. It is of great significance to reduce the patient's response to treatment, improve the prognosis of patients, reduce the risk of cancer recurrence and metastasis, and bring greater well-being to patients.

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Ethics approval

This study is not subject to any ethical standards

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