Heliyon 10 (2024) e27437

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Review article

Global biomarker trends in Parkinson's disease research: A bibliometric analysis

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ARTICLE INFO

Keywords:
Parkinson's disease
Dementia
Biomarker research
WOS
Bibliometric

ABSTRACT

As the second most common neurodegenerative disease globally, Parkinson's disease (PD) affects millions of people worldwide. In recent years, the scientific publications related to PD biomarker research have exploded, reflecting the growing interest in unraveling the complex pathophysiology of PD. In this study, we aim to use various bibliometric tools to identify key scientific concepts, detect emerging trends, and analyze the global trends and development of PD biomarker research.The research encompasses various stages of biomarker development, including exploration, identification, and multi-modal research. MOVEMENT DISORDERS emerged as the leading journal in terms of publications and citations. Key authors such as Mollenhauer and Salem were identified, while the University of Pennsylvania and USA stood out in collaboration and research output. NEUROSCIENCES emerged as the most important research direction. Key biomarker categories include α-synuclein-related markers, neurotransmitter-related markers, inflammation and immune system-related markers, oxidative stress and mitochondrial function-related markers, and brain imaging-related markers. Furthermore, future trends in PD biomarker research focus on exosomes and plasma biomarkers, miRNA, cerebrospinal fluid biomarkers, machine learning applications, and animal models of PD. These trends contribute to early diagnosis, disease progression monitoring, and understanding the pathological mechanisms of PD.

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder characterized by motor symptoms such as tremors, rigidity, and bradykinesia, as well as non-motor symptoms including cognitive impairment, depression, and sleep disturbances [1,2]. As the second most common neurodegenerative disorder worldwide, PD is estimated to affect over 6 million people globally, imposing a significant burden on both health and economy [3,4]. Early-stage Parkinson's disease is difficult to detect and progresses slowly, leading to potential misdiagnosis or underdiagnosis. This highlights the need for prompt and accurate diagnosis to effectively manage the disease [5]. Currently, diagnosis predominantly relies on clinical assessment, which is subjective and limited to the observation of motor symptoms. Consequently, there is an urgent need to identify reliable biomarkers to aid in the early detection and monitoring of PD.

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https://doi.org/10.1016/j.heliyon.2024.e27437
Received 14 September 2023; Received in revised form 11 December 2023; Accepted 28 February 2024
Available online 6 March 2024

Advances in biomedical research and technology have paved the way for the identification and exploration of various potential biomarkers for PD [6]. High-throughput omics technologies, such as genomics, transcriptomics, proteomics, and metabolomics, enable researchers to investigate molecular alterations associated with PD on a global scale [7–10]. Furthermore, neuroimaging techniques such as magnetic resonance imaging (MRI) and positron emission tomography (PET) offer profound insights into the structural and functional changes in the brains of PD patients [11,12].

In recent years, there has been a significant increase in scientific publications in the field of PD biomarker research, reflecting the growing interest and efforts in understanding the complex pathophysiology of PD. In this study, our aim is to analyze the global trends and developments in PD biomarker research using bibliometric tools such as CiteSpace, VOSviewer, and Scimago Graphica. These tools harness the power of natural language processing and data visualization to identify key scientific concepts, detect emerging trends, and map the collaborative networks within the research community. Through conducting a comprehensive bibliometric analysis, we aim to gain in-depth insights into the current status of PD biomarker research, including the most influential researchers, prolific institutions, and highly cited articles. Additionally, we aim to identify emerging research topics and potential knowledge gaps within this field. This knowledge will not only assist researchers and clinicians in keeping up with the latest advancements but also guide future research directions, ultimately leading to the development of more accurate diagnostic tools and innovative therapeutic strategies for PD.

2. Data collection and analysis

Search the Web of Science (WOS) Core Collection database (www.webofscience.com). The literature search was conducted using the following framework: (TS=(Idiopathic Parkinson's Disease) OR TS=(Lewy Body Parkinson's Disease) OR TS=(Parkinson's Disease, Idiopathic) OR TS=(Parkinson's Disease, Lewy Body) OR TS=(Parkinson Disease, Idiopathic) OR TS=(Parkinson's Disease) OR TS=(Idiopathic Parkinson Disease) OR TS=(Lewy Body Parkinson Disease) OR TS=(Primary Parkinsonism) OR TS=(Parkinsonism, Primary) OR TS=(Paralysis Agitans))AND (TS = (biomarker*)). DTT and LXH independently conducted an automated deduplication process, and in conjunction with manually reading the titles and abstracts of the literature, excluded irrelevant papers related to PD biomarker research. In case of literature discrepancies, YJG and LYX assisted in resolving them. The search was conducted from the inception of the database until 2023-07-30. The publication types were restricted to Article and Review Article, and the language was limited to English. WXX conducted a secondary review of the literature and ultimately included 643 relevant studies. The specific process is illustrated in Fig. 1. WXX exported the included literature with Author(s), Title, Source, Times Cited Count, and other 29 attributes in Refworks and Excel formats, respectively. CiteSpace, VOSviewer, and Scimago Graphica were utilized to extract potential knowledge information from the literature on PD biomarkers as data resources. The data was transformed into panoramic images to analyze the global development trends, research hotspots, and potential trends of PD biomarkers.

3. Trends related to Parkinson's disease biomarkers

3.1. Articles

A total of 643 included publications were cited 22,138 times. The most highly cited publication is "Detection of oligomeric forms of alpha-synuclein protein in human plasma as a potential biomarker for Parkinson's disease" by El-Agnaf, Omar M. A. (587 citations, IF = 4.8, Q2), followed by "DJ-1 and alpha-synuclein in human cerebrospinal fluid as biomarkers of Parkinson's disease" (493 citations, IF = 14.5, Q1), "Cognitive impairment in patients with Parkinson's disease: diagnosis, biomarkers, and treatment" (367 citations, IF = 48, Q1), "Metabolomic profiling to develop blood biomarkers for Parkinson's disease" (344 citations, IF = 14.5, Q1), and "Is alpha-synuclein in the colon a biomarker for premotor Parkinson's Disease? Evidence from 3 cases" (310 citations, IF = 8.6, Q1). All of

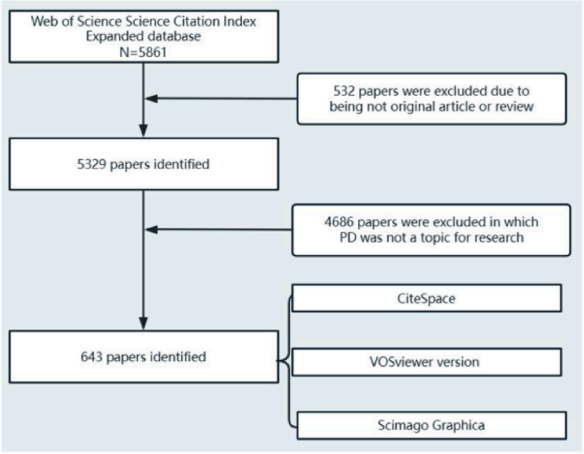

Fig. 1. Flowchart of literature screening.

these articles were cited more than 300 times. Highly cited literature sources have higher impact factors, indicating their authority in the field of PD biomarkers. However, despite being widely cited, these studies have not been replicated in other research. We believe this may be related to factors such as the interests, methods, and technical limitations within the academic community, as well as the complexity and varied research objectives of the studies. For example, one of the most extensively cited studies developed a new ELISA method to detect the oligomeric forms of alpha-synuclein protein in plasma samples of Parkinson's disease patients, suggesting the potential of these oligomers as biomarkers for Parkinson's disease. This study garnered significant attention in the academic community. However, it also has some limitations. Firstly, the sample size was small, with only a few individuals being tested. Secondly, the ELISA method used has certain limitations, such as its ability to only identify the oligomeric forms of alpha-synuclein protein and not other possible aggregated states. Therefore, further research with larger sample sizes and more accurate methods is needed to determine more conclusively whether alpha-synuclein protein can serve as a diagnostic biomarker for Parkinson's disease.

3.2. Year of publication and citation

Fig. 2 depicts the annual publication volume, Times Cited, All Databases, and 180 Day Usage Count of the included literature. From the figure, we can observe the development of PD biomarkers, which can be divided into three stages: Exploration stage (2000–2010): Researchers began to explore and identify potential PD biomarkers. The focus of the research included indicators such as proteins and metabolites in serum, cerebrospinal fluid, and other body fluids. However, progress was relatively slow due to technological limitations and limited research samples. Biomarker identification stage (2010–2015): With the development of technology and an increase in the number of samples, researchers started to identify some potential biomarkers. These include proteins like α-synuclein and DJ-1, which may be associated with the development and pathological processes of PD. Multi-modal biomarker research stage (2015 to present): In recent years, the study of PD biomarkers has gradually shifted towards more comprehensive and diverse research methods. For example, a combination analysis is conducted by integrating multiple biomarkers such as protein markers and metabolites to improve the accuracy of diagnosis and monitoring. Additionally, other modal biomarkers, such as neuroimaging indicators, have been studied to assist in the diagnosis and evaluation of the disease.

3.3. Distribution per journal

We included the literature into VOSviewer version and identified a total of 245 journals that published relevant research. The largest cluster of interconnections among these journals consisted of 201 journals (Fig. 3A), indicating significant interdisciplinary collaboration in this field. We displayed the top 10 journals by publication count (Fig. 3B). The journal with the highest publication count was "MOVEMENT DISORDERS" (N = 41), followed by "JOURNAL OF PARKINSON'S DISEASE" (N = 26), "PARKINSONISM & RELATED DISORDERS" (N = 24), "FRONTIERS IN AGING NEUROSCIENCE" (N = 23), and "PLOS ONE" (N = 21). These journals play important roles in the research in this field. "MOVEMENT DISORDERS" also had the highest total citation count (N = 2428). On the other hand, "ACS NANO" had the highest average citations per paper (1 paper, 249 citations). Fig. 3C shows the core journals in PD biomarkers, which have a leading and exemplary role in this field. Additionally, "NPJ PARKINSON'S DISEASE," "BRAIN SCIENCES," and "AGEING RESEARCH REVIEWS" are emerging journals with a higher publication count in recent years (Fig. 3D).

To further elucidate the academic interaction and knowledge dissemination patterns between different journals, we constructed a dual-journal overlay map (Fig. 4). This map illustrates the citation paths between different journals and their application significance in the field of PD biomarkers. Fig. 4 reveals three main citation paths: MOLECULAR/BIOLOGY/IMMUNOLOGY→MOLECULAR/BIOLOGY/GENETICS (z = 7.3874, f = 7792); MOLECULAR/BIOLOGY/IMMUNOLOGY→PSYCHOLOGY/EDUCATION/SOCIAL (z =

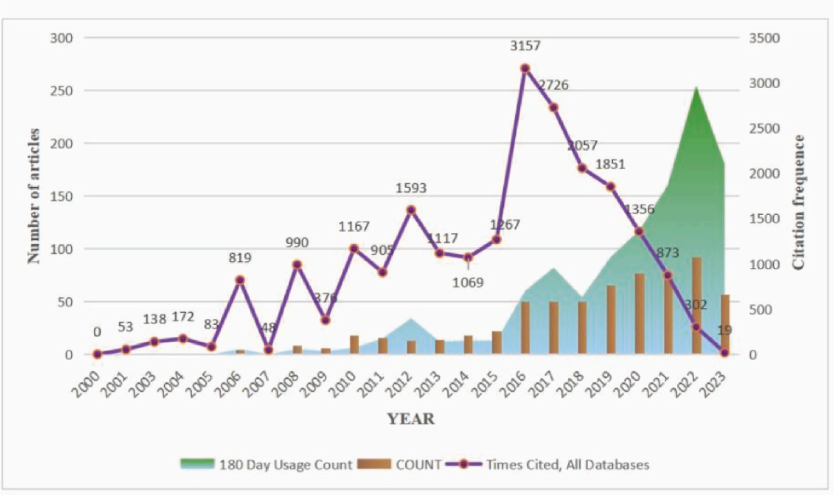

Fig. 2. Year of publication and citation.

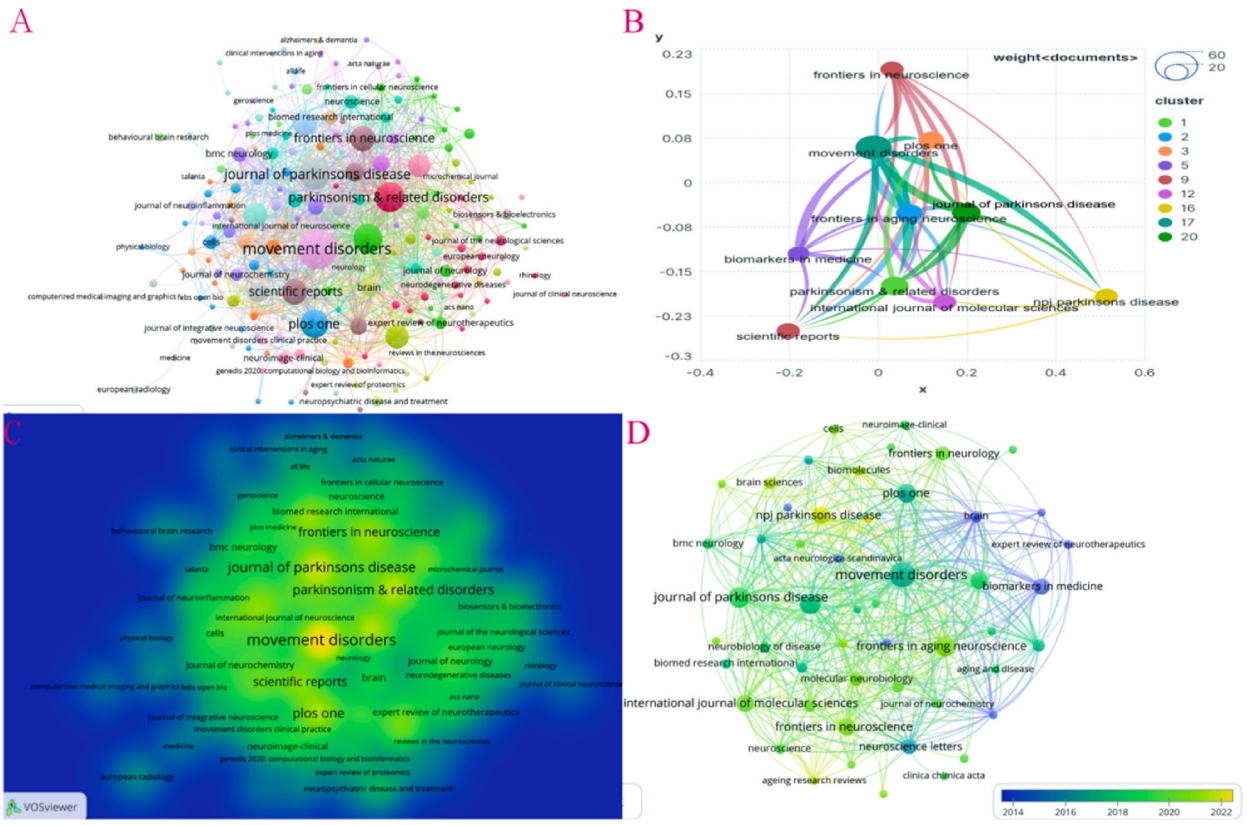

Fig. 3. Journal network visualization of PD biomarker literature.

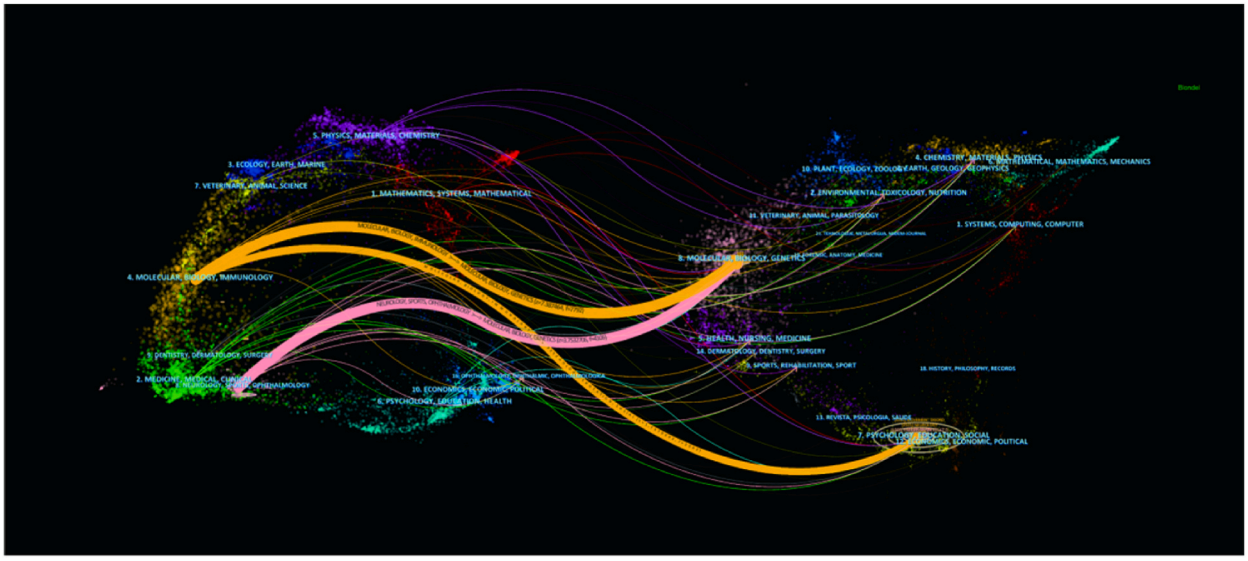

Fig. 4. CiteSpace-based dual map overlay of journals connected to the PD biomarker field.

1.7380, f = 2062); NEUROLOGY/SPORTS/OPHTHALMOLOGY→MOLECULAR/BIOLOGY/GENETICS (z = 3.7533, f = 4106). The map uncovers the crucial citation paths and associations with PD biomarkers, providing researchers with opportunities for collaboration and exchange, and guiding them towards cutting-edge research in this field.

3.4. Author and co-author analysis

We used VOSviewer version software for the analysis of authors and co-authors. To avoid uncertainty caused by author abbreviations, we modified the shortened author names, such as changing “Salem, SA” to “Salem, Sultan A.” We found that a total of 4066 authors participated in PD biomarkers research. The largest cluster of interconnected projects consisted of 1057 projects (Fig. 5A), indicating the level of collaboration and closeness in the field of PD biomarkers research. In Fig. 5A, the largest network was formed around Mollenhauer, Brit, comprising 80 individuals with a total link strength of 232. Fig. 5B displays the author relationship graph for authors with a publication count of ≥6. Mollenhauer, Brit had the highest number of papers (N = 19), followed by Zhang, Jing (N = 12) and Marek, Kenneth (N = 10). The author with the highest total citation count was Mollenhauer, Brit (N = 1308). Salem, Sultan A. had the highest average citations per paper (1 paper, 555.00 citations). Mollenhauer, Brit, Frasier, Mark, and Zhang, Jin were the core authors in this field (Fig. 5C), playing a leading and exemplary role in PD biomarkers research. Foroud, Tatiana [13,14], Lingor, Paul [15–18], and Siderowf, Andrew [14,19–21] were emerging scholars with significant recent publications (Fig. 5D). They have been driving research progress in this field through studying different body fluids, multicenter collaborations, and connections with other diseases. These studies have important potential implications for the improvement of early diagnosis, monitoring, and treatment strategies for Parkinson’s disease.

3.5. Distribution of countries/regions and institutions

3.5.1. Countries/regions

We analyzed the publication countries using VOSviewer version and Scimago Graphica software. To eliminate uncertainty in country names, we modified them according to the naming conventions of Scimago Graphica software, for example, changing “England”, “Scotland”, “Wales”, and “Northern Ireland” to “United Kingdom.” A total of 56 countries/regions participated in PD biomarkers research, forming 8 major clusters (Fig. 6A). USA established the largest national collaboration network, involving 35 countries, followed by Germany (N = 30), China (N = 26), and Italy (N = 26). The country with the highest number of publications was USA (N = 175), followed by China (N = 168) and Germany (N = 70). USA had the highest total citation count (N = 8458), followed by China (N = 3962) and United Kingdom (N = 3799). USA, Germany, China, and Italy were the core countries in this field (Fig. 6B), leading in terms of research and achievements in PD biomarkers. These countries have actively explored, innovated, and made significant breakthroughs in PD biomarkers research. Taking the USA as an example, it has a leading position in advanced imaging

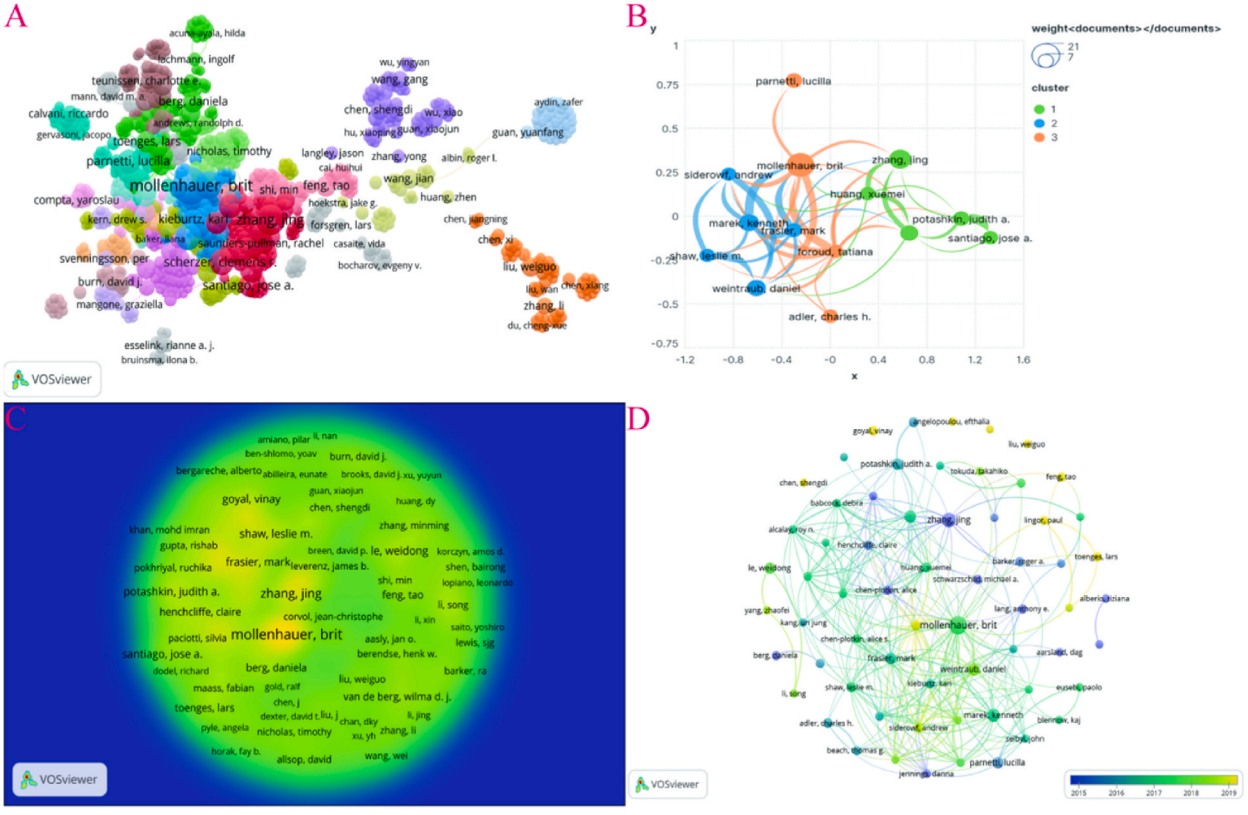

Fig. 5. Network visualization of PD biomarker paper s.

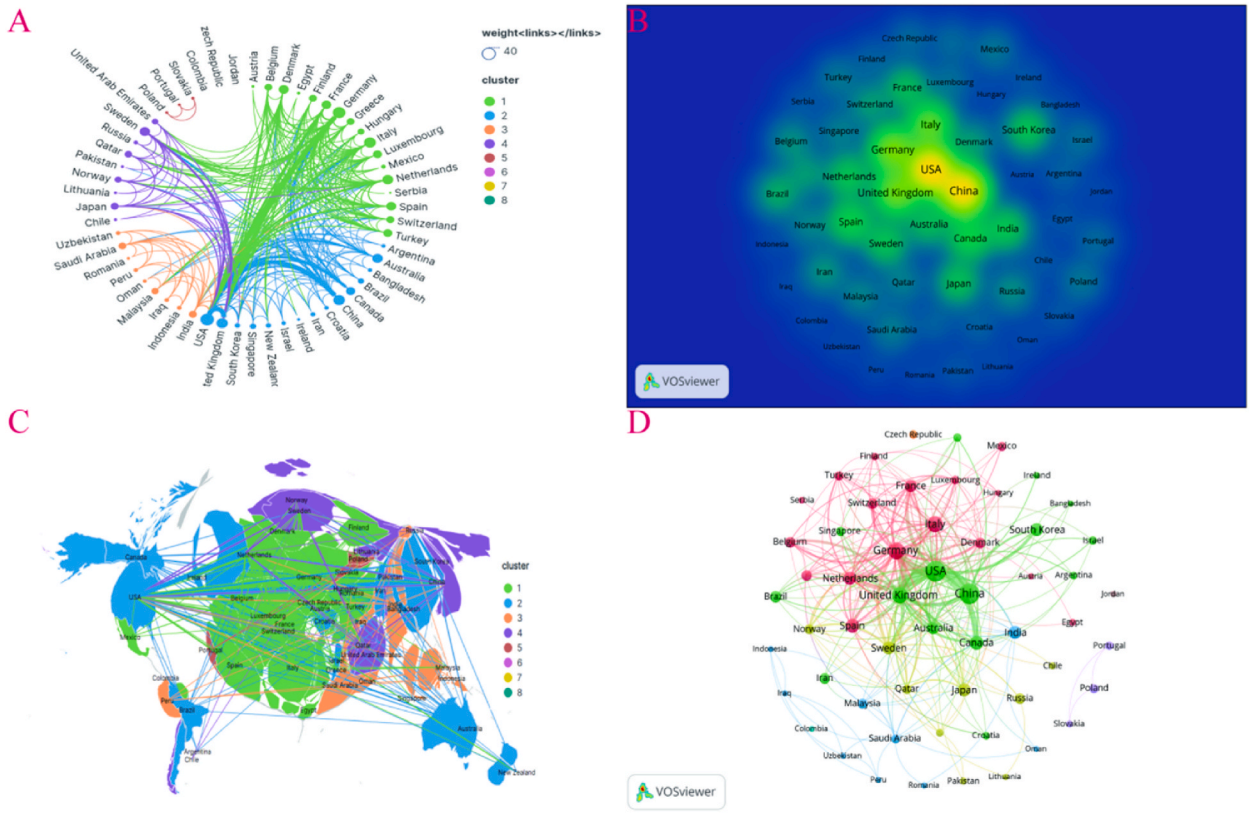

Fig. 6. The network displays collaborations between countries/regions in PD biomarker research.

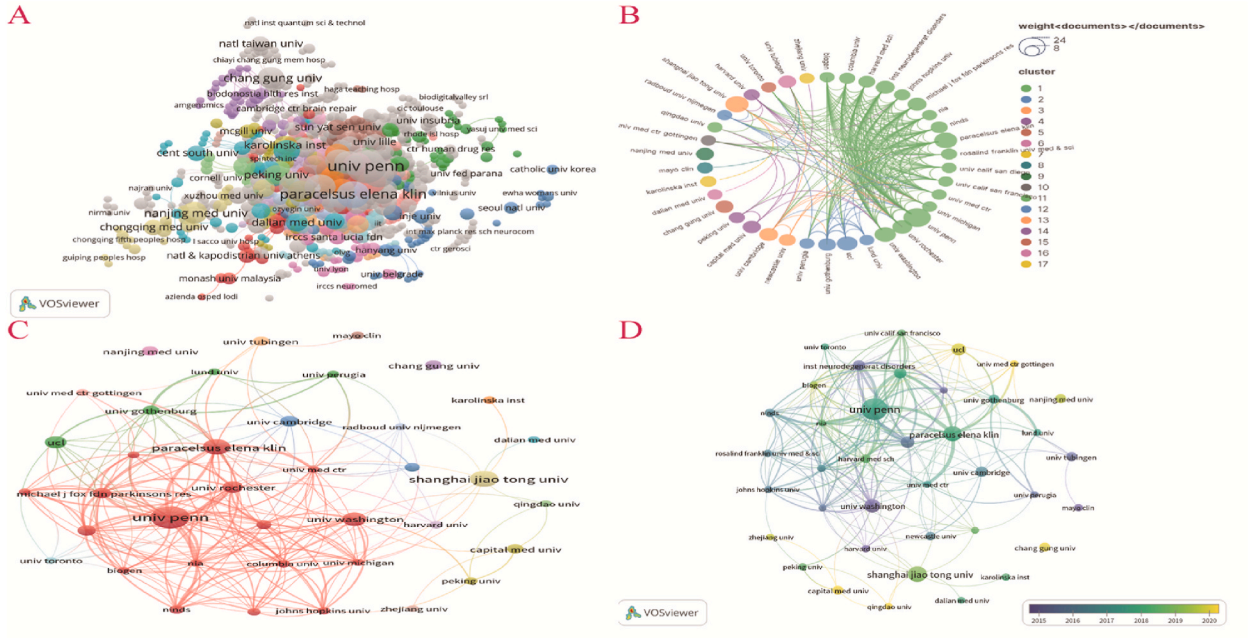

Fig. 7. Network visualization of institutions in PD biomarker research.

techniques, genomics, and proteomics, which have led to the discovery of multiple potential PD biomarkers. Germany has explored the biological mechanisms and biomarker characteristics of PD through innovative technologies such as genetic analysis, brain imaging, and protein analysis. China has utilized its large population resources to drive large-scale studies and accelerate the discovery and validation of PD biomarkers. Italy has deepened the understanding of PD biomarkers through multidisciplinary collaborations, combining clinical data, brain imaging, and biosamples, and promoted their application in clinical practice. The outstanding contributions, characteristics of these four countries, as well as their cooperation and exchanges, have collectively propelled the progress of PD biomarkers research and global collaboration (Fig. 6C,D). Through their efforts, we are able to better understand and address this complex disease, Parkinson's disease.

3.5.2. Institutions

We analyzed the publication institutions using VOSviewer version and Scimago Graphica software, and a total of 1231 institutions participated in the research. The largest associated network among the 1231 institutions consists of 894 institutions, organized into 39 major clusters (Fig. 7A). University of Pennsylvania constructed the largest collaboration network with a link of 118 and a total link strength of 222, followed by University of Rochester and Paracelsus Elena Klin. Fig. 7B and C displays the institutions with a publication count of $\geq$7, with University of Pennsylvania having the highest publication count (N = 23), followed by Shanghai Jiao Tong University (N = 17) and Paracelsus Elena Klin (N = 16). The institutions with the highest citation counts are University of Pennsylvania (N = 1327), followed by Univ Washington (N = 1190) and Paracelsus Elena Klin (N = 1077). University College London (UCL), capital med univ, and univ med ctr gottingen have published a significant number of papers in recent years (Fig. 7D). University College London explores the biological mechanisms of PD and seeks potential biomarkers using advanced brain imaging techniques, genomics, and proteomics. Capital Medical University, as an important medical university in China, actively participates in PD biomarker research and explores the relationship with genetics and biomarkers. University Medical Center Göttingen, as an important medical center in Germany, delves into the biological mechanisms of PD occurrence and development through clinical samples and molecular biology techniques, and collaborates with other institutions to promote PD biomarker research.

3.6. Research areas

The included literature can be divided into 66 research topics according to WOS categories (Table 1), and these classifications reflect the importance and focus of different research fields. Among them, "NEUROSCIENCES" (N = 276) is the most important research direction, focusing on important issues and advancements in the field of neuroscience. "CLINICAL NEUROLOGY" (N = 174) focuses on research and practice in clinical neurology. "BIOCHEMISTRY & MOLECULAR BIOLOGY" (N = 66) focuses on research in biochemistry and molecular biology. These classifications provide us with clues to better understand the importance and development directions of various fields.

3.7. Keywords co-occurrence, clusters and bursts

We analyzed the keywords using CiteSpace software, and a total of 643 keywords were included in the literature (Table 2, Fig. 8A). The most common terms are parkinsons disease (N = 393), alzheimers disease (N = 169), cerebrospinal fluid (N = 165), and alpha synuclein (N = 156). We classified the PD biomarkers mentioned in the keywords into five categories, as follows: ① α-synuclein-related markers: Alpha synuclein (N = 156), Lewy body (N = 40), Alpha synuclein expression (N = 14); ② Neurotransmitter-related markers: Dopaminergic neuron (N = 13), Dopamine transporter (N = 5), Cerebrospinal fluid biomarker (N = 26); ③ Inflammation and immune system-related markers: TNF alpha (N = 5), Microglial activation (N = 4), Cytokine (N = 4); ④ Oxidative stress and mitochondrial function-related markers: Oxidative stress (N = 47), Mitochondrial dysfunction (N = 4), Lipid peroxidation (N = 3); ⑤ Brain imaging-related markers: Magnetic resonance imaging (N = 11), Positron emission tomography (N = 5), Transcranial sonography (N = 2). Additionally, the keywords also reflect the authors' focus on the diagnosis and disease characteristics of Parkinson's disease (diagnosis, mild cognitive impairment, lewy body), disease progression and pathology (progression, neurodegeneration, pathology), risk and association (risk, association, risk factor), as well as treatment and intervention (deep brain stimulation, levodopa, drug-naive patient).

Table 1
Top 10 WOS categories for PD biomarker literature.

WoS Categories	number
NEUROSCIENCES	276
CLINICAL NEUROLOGY	174
BIOCHEMISTRY & MOLECULAR BIOLOGY	66
MULTIDISCIPLINARY SCIENCES	45
MEDICINE, RESEARCH & EXPERIMENTAL	45
GERIATRICS & GERONTOLOGY	38
CELL BIOLOGY	29
CHEMISTRY, MULTIDISCIPLINARY	23
PHARMACOLOGY & PHARMACY	21
CHEMISTRY, ANALYTICAL	15

Table 2
Top 12 co-occurring keywords in PD biomarker literature.

Rank	Keywords	Year	Count
1	neuromyelitis optica	2006	87
2	multiple sclerosis	2006	67
3	diagnostic criteria	2008	28
4	aquaporin 4	2006	25
5	marker	2006	25
6	anti aquaporin 4 antibody	2010	18
7	antibody	2008	17
8	cerebrospinal fluid	2008	17
9	aquaporin-4 immunoglobulin g	2007	15
10	biomarker	2010	13
11	disease	2004	12
12	lesions	2007	11

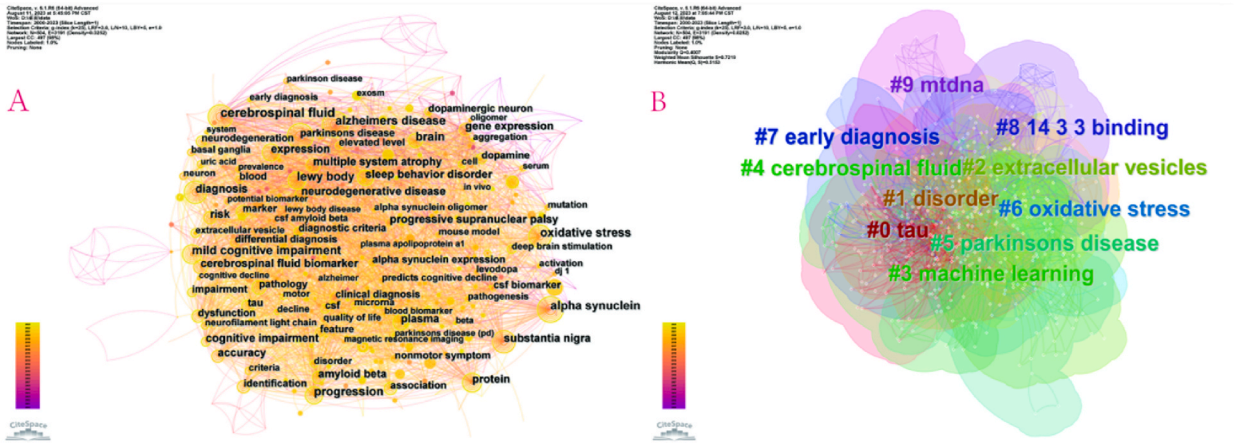

Fig. 8. Network visualization and clustering analysis of keywords in PD biomarker research papers.

Table 3
Clustering analysis of keywords in PD biomarker literature.

ClusterID	Size	Silhouette	Mean (Year)	Label (LLR)
0	92	0.667	2013	tau (25.65, 1.0E-4); csf biomarkers (22.11, 1.0E-4); mild cognitive impairment (21.72, 1.0E-4); dementia (16.43, 1.0E-4); cerebrospinal fluid biomarker (14.73, 0.001)
1	77	0.559	2013	disorder (11.69, 0.001); immunoassay (7.79, 0.01); clinical diagnosis (7.79, 0.01); marker (7.79, 0.01); discovery (7.79, 0.01)
2	46	0.74	2018	extracellular vesicles (18.24, 1.0E-4); parkinson's disease (15.33, 1.0E-4); parkinson disease (11.8, 0.001); cerebrospinal fluid (9.77, 0.005); peripheral blood (8.36, 0.005)
3	44	0.706	2018	machine learning (26.42, 1.0E-4); deep brain stimulation (18.61, 1.0E-4); blood biomarkers (15.7, 1.0E-4); subthalamic nucleus (10.46, 0.005); white matter (6.79, 0.01)
4	44	0.812	2007	cerebrospinal fluid (18.31, 1.0E-4); positron emission tomography (14.08, 0.001); alpha synuclein (9.77, 0.005); differential diagnosis (9.45, 0.005); dopamine transporter (7.85, 0.01)
5	42	0.759	2016	parkinson's disease (pd) (16.24, 1.0E-4); cognitive dysfunction (9.01, 0.005); magnetic resonance imaging (mri) (9.01, 0.005); quality of life (7.37, 0.01); magnetic resonance imaging (6.92, 0.01)
6	40	0.747	2013	oxidative stress (15.79, 1.0E-4); microglia (7.51, 0.01); urate (7.51, 0.01); reactive oxygen species (5.91, 0.05); drug development (5.91, 0.05)
7	39	0.762	2015	early diagnosis (10.2, 0.005); biomedical analysis (8.98, 0.005); biotechnology (8.98, 0.005); copy number (6.35, 0.05); nafd pathway (6.35, 0.05)
8	38	0.787	2014	14 3 3 binding (26.51, 1.0E-4); phosphorylation (23.13, 1.0E-4); in vivo (15.88, 1.0E-4); mutation (13.85, 0.001); parkinson' (12.22, 0.001)
9	21	0.882	2006	parkinson's disease (28.54, 1.0E-4); tau (7.72, 0.01); cerebrospinal fluid (7.38, 0.01); mtdna (7.28, 0.01); striatum (7.28, 0.01)

Through keyword clustering, we can gain a comprehensive understanding of the thematic structure and research hotspots in Parkinson's disease biomarker studies (Table 3, Fig. 8B). Cluster 0 mainly involves keywords such as tau, csf biomarkers, mild cognitive impairment, dementia, and cerebrospinal fluid biomarker. This indicates that researchers focus on the role of tau protein in

Parkinson's disease and the application of cerebrospinal fluid biomarkers in early cognitive dysfunction and dementia. Cluster 1 involves keywords such as disorder, immunoassay, clinical diagnosis, marker, and discovery. This cluster demonstrates a focus on immune assay techniques for Parkinson's disease diagnosis and the discovery of new markers. Cluster 2 involves keywords such as extracellular vesicles, parkinson's disease, parkinson disease, cerebrospinal fluid, and peripheral blood. This cluster explores the role of extracellular vesicles in Parkinson's disease and the possibility of studying Parkinson's disease through cerebrospinal fluid and peripheral blood samples. Cluster 3 involves keywords such as machine learning, deep brain stimulation, blood biomarkers, subthalamic nucleus, and white matter. This cluster focuses on the application of machine learning in Parkinson's disease and the study of Parkinson's disease through blood biomarkers, deep brain stimulation, subthalamic nucleus, and white matter. Cluster 4 mainly involves keywords such as cerebrospinal fluid, positron emission tomography, alpha synuclein, differential diagnosis, and dopamine transporter. This cluster focuses on the potential role of cerebrospinal fluid biomarkers, positron emission tomography, and related proteins such as alpha synuclein in the differential diagnosis of Parkinson's disease. Additionally, there are cluster 5 (parkinsons disease (pd)), cluster 6 (oxidative stress), cluster 7 (early diagnosis), cluster 8 (14 3 3 binding), cluster 9 (mtdna), cluster 10 (geographic information systems (gis)), and cluster 11 (animal models).

We analyzed the modification trends and emergence time of 643 keywords using CiteSpace software (Figs. 9 and 10). Cerebrospinal fluid, Alzheimer's disease, and alpha-synuclein have always been research focuses in the field of PD biomarkers. In recent years, researchers have started to pay attention to tumor necrosis factor, immune infiltration, and neuroinflammation. However, our analysis revealed that imaging techniques such as MRI and PET/SPECT, which serve as crucial biomarkers for Parkinson's disease, did not exhibit a significant increase in keyword occurrence and modification throughout the process. We posit that this may be attributed to the limitations imposed by our search scope and methodology, which hindered a comprehensive comprehension of these imaging technologies. Nevertheless, our analysis underscores the continued significance of imaging techniques in Parkinson's disease and highlights their substantial potential for further advancement in future research. This implies that there is a need for increased emphasis on multi-source retrieval and comprehensive analysis techniques when conducting bibliometric analysis. Simultaneously, it is crucial to remain attentive to the latest advancements and trends in Parkinson's disease research in order to enhance comprehension of the application and significance of diverse biomarkers within this domain, thereby fostering advancements in the diagnosis and treatment of Parkinson's disease.

3.8. Co-cited articles and co-cited reference cluster analysis

In 1973, Small first proposed the concept of Co-citation in literature, which can explore the development and evolutionary dynamics of PD biomarkers. We used CiteSpace software to analyze the included literature. Fig. 11 shows the most frequently cited references in PD biomarker articles. Further clustering the references, we identified four major domains of PD biomarkers: #0 "dj-1", #1 "extracellular vesicles", #3 "molecular imaging", and #4 "cerebrospinal fluid"(Table 4).

These domains are all associated with keyword clustering and literature co-citation clustering. By comparing the content of

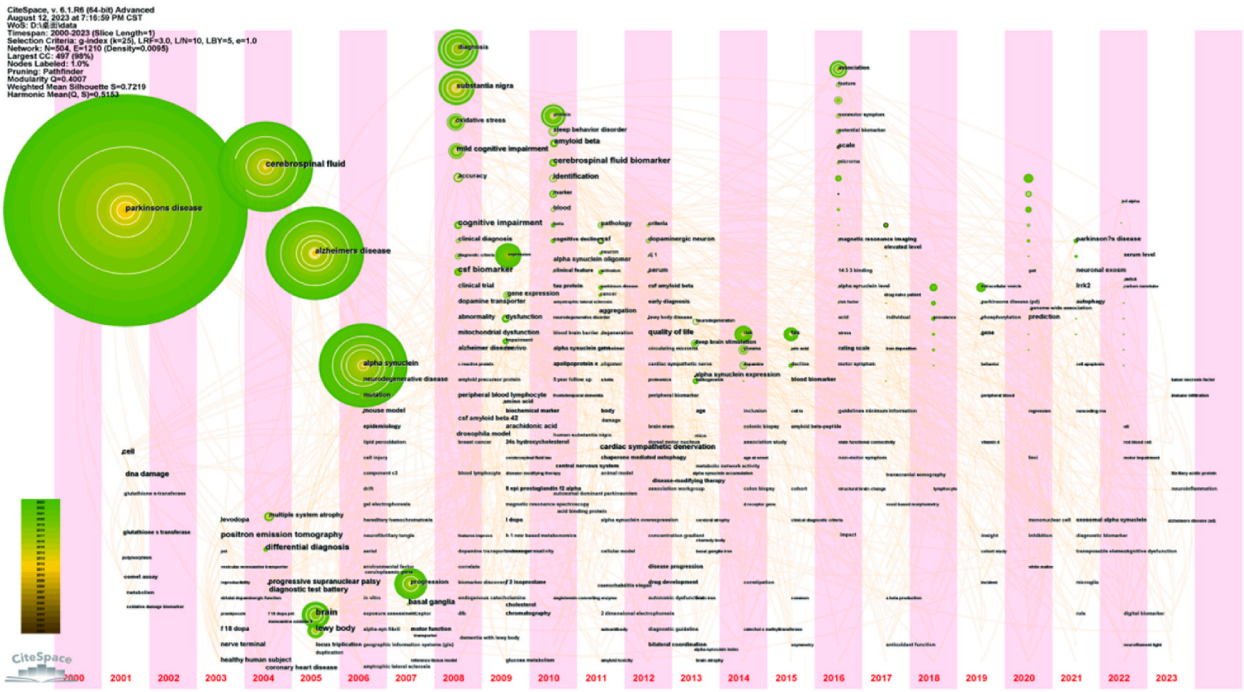

Fig. 9. Analysis of yearly changes in keywords of PD biomarker research papers.

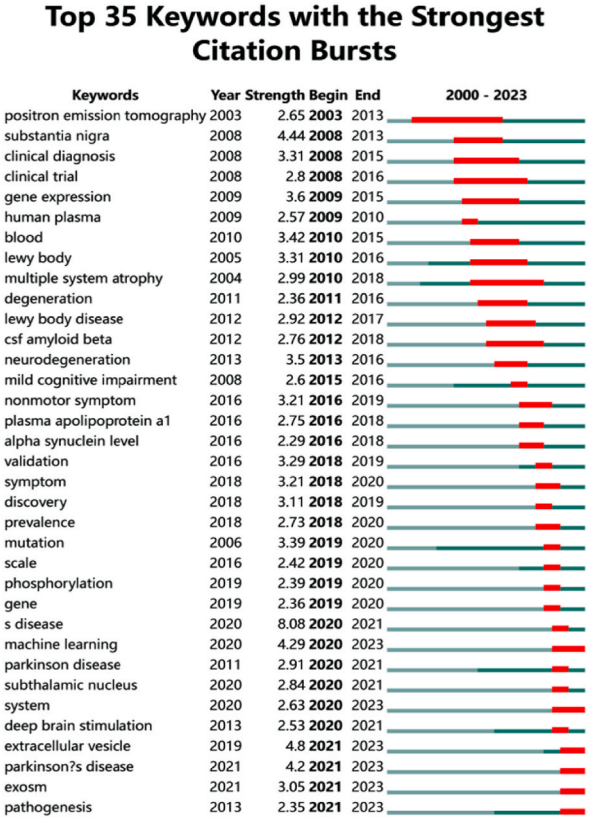

Fig. 10. Burst map of keywords in PD biomarker research papers.

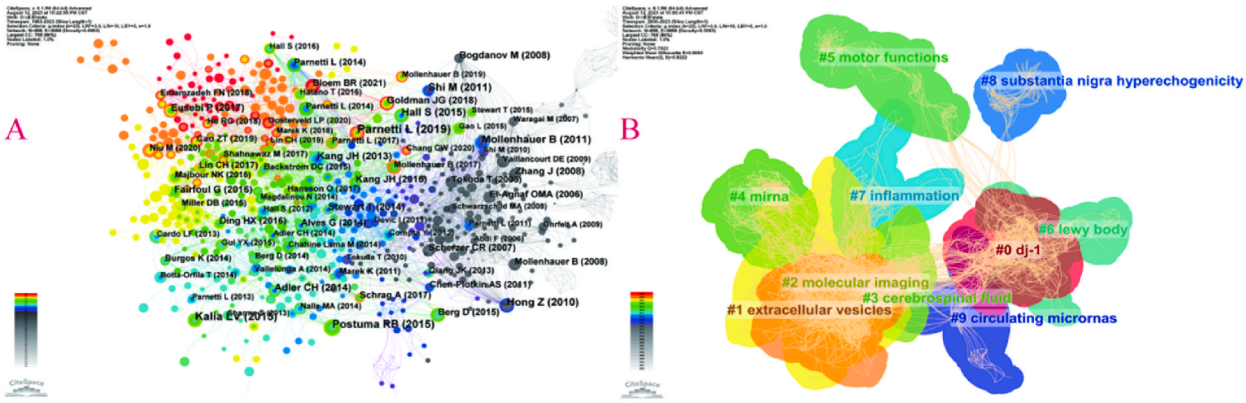

Fig. 11. Co-citation of references and clustering analysis of co-cited references in PD biomarker research papers.

keyword clustering and literature co-citation clustering, we have drawn some important conclusions and insights. Firstly, Cluster 2 in keyword clustering and Cluster 1 in literature co-citation clustering both highlight keywords such as "extracellular vesicles," "parkinson's disease," and "plasma biomarker". This indicates a high correlation between the research on extracellular vesicles, PD, plasma biomarkers, and the field of PD biomarker study. This finding can further promote the potential research direction of using extracellular vesicles as PD biomarkers. Secondly, Cluster 5 in keyword clustering and Cluster 4 in literature co-citation clustering both highlight keywords such as "miRNA" and "alzheimer's disease". This suggests a close association between miRNA research and Alzheimer's disease in PD research. This finding provides a new perspective to further study the pathological mechanisms of PD and the discovery of biomarkers from the perspective of miRNA.In addition, Cluster 4 in keyword clustering and Cluster 3 in literature co-citation clustering both emphasize keywords such as "cerebrospinal fluid", indicating the important role of cerebrospinal fluid in PD biomarker research. This finding can promote further research on biomarkers in cerebrospinal fluid and explore their application in

Table 4
Cluster analysis of co-cited literature for PD biomarkers.

Cluster	Size	Year	LLR
0	122	2008	dj-1 (15.98, 1.0E-4); premotor (8.41, 0.005); parkin (8.41, 0.005); neuroprotection (8.41, 0.005); proteomics (7.48, 0.01)
1	109	2018	extracellular vesicles (17.32, 1.0E-4); parkinson's disease (14.1, 0.001); plasma biomarker (7.03, 0.01); systematic review (7.03, 0.01); parkinsons disease (pd) (7.03, 0.01)
2	108	2014	extracellular vesicles (6.22, 0.05); molecular imaging (6.19, 0.05); magnetic resonance imaging (mri) (6.19, 0.05); vision (6.19, 0.05); neuromelanin (6.19, 0.05)
3	91	2014	cerebrospinal fluid (10.22, 0.005); tau proteins (7.11, 0.01); longitudinal (7.11, 0.01); cerebrospinal fluid biomarkers (7.11, 0.01); amyloid-beta (6.55, 0.05)
4	68	2016	mirna (14.87, 0.001); lncrna (11.96, 0.001); microrna (11.71, 0.001); micrornas (7.96, 0.005); alzheimers disease (6.56, 0.05)
5	58	2002	motor functions (9.08, 0.005); prodrome (9.08, 0.005); neuropsychology (9.08, 0.005); [c-11]beta-cft (9.08, 0.005); lewy body dementia (9.08, 0.005)
6	57	2008	lewy body (8.66, 0.005); biomarker (6.85, 0.01); animal models (6.17, 0.05); neuroprotective drugs (6.17, 0.05); huntingtons disease (6.17, 0.05)
7	51	2018	inflammation (5.47, 0.05); regression analysis (5.36, 0.05); chemometrics (5.36, 0.05); computational approach (5.36, 0.05); cohort studies (5.36, 0.05)
8	36	2002	substantia nigra hyperechogenicity (10.1, 0.005); ceruloplasmin (10.1, 0.005); iron (7.34, 0.01); transcranial ultrasound (6.31, 0.05); diagnosis (3.06, 0.1)
9	27	2010	circulating micrornas (8, 0.005); blood biomarkers (8, 0.005); 2d-dige (8, 0.005); network analysis (8, 0.005); hnf4a (8, 0.005)

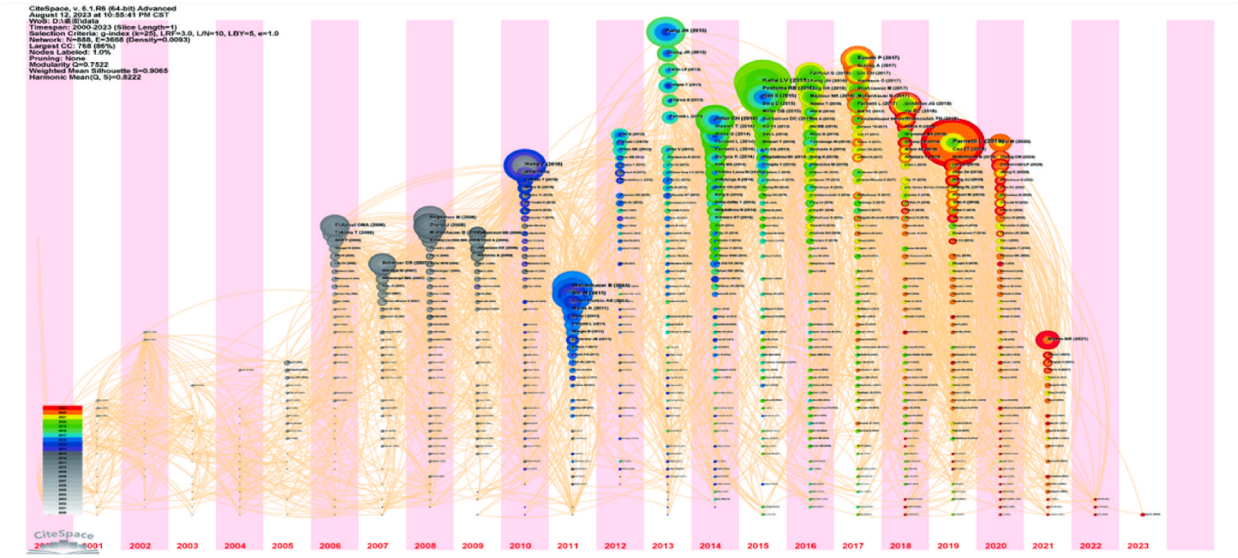

Fig. 12. Temporal map of co-cited references in PD biomarker research papers.

early diagnosis and disease progression monitoring of PD.

Fig. 12 shows the evolutionary process of co-cited references in the included literature. The use of CiteSpace software revealed the most impactful citations in the past decade (Fig. 13). Table 5 lists the highly cited references in the field of PD biomarkers. These findings provide important insights and directions for the research and application of PD biomarkers.

4. Research hotspots and future trends

By analyzing the literature on PD biomarkers,the following research hotspots and future trends can be identified：

4.1. Research hotspots

① Study on α-synuclein-related markers: Researchers focus on the role of α-synuclein in Parkinson's disease and its related markers, such as Lewy bodies and α-synuclein expression [5,13,22–26].② Discovery of neurotransmitter-related markers: Researchers are focusing on markers related to neurotransmitters, such as dopamine neurons, dopamine transporters, and cerebrospinal fluid biomarkers, which are of significant diagnostic value in Parkinson's disease [7,9,14,15].③ Study on oxidative stress and mitochondrial function: Researchers focus on markers related to oxidative stress, mitochondrial dysfunction, and lipid peroxidation, which suggests that mitochondrial function may play a critical role in the pathogenesis of Parkinson's disease [27–29].④ Study on the immune system and inflammation: Researchers are focusing on markers related to inflammation and the immune system, such as TNF-alpha, microglial

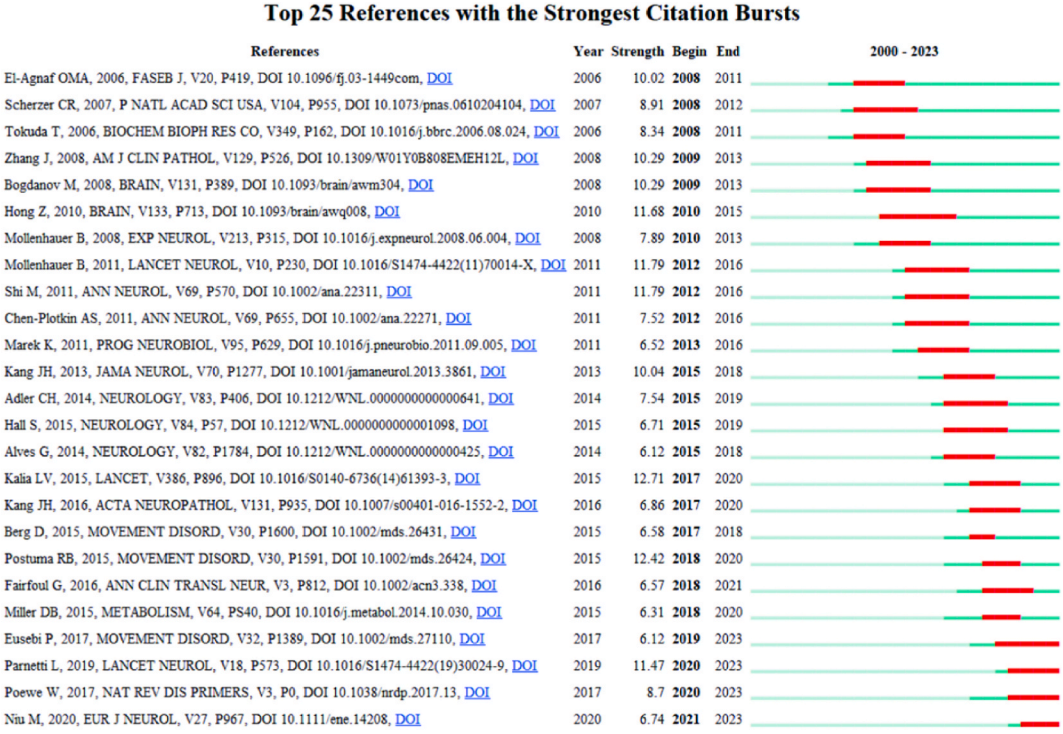

Fig. 13. Top 25 most cited references in PD biomarker research papers.

Table 5
Top 10 highly cited references in PD biomarker papers.

Citation	Year	First author	Journal	Title
39	2019	Parnetti L	LANCET NEUROL	CSF and blood biomarkers for Parkinson's disease
35	2015	Kalia LV	LANCET	Parkinson's disease
32	2015	Postuma RB	MOVEMENT DISORD	MDS clinical diagnostic criteria for Parkinson's disease
28	2015	Hall S	NEUROLOGY	CSF biomarkers and clinical progression of Parkinson disease
26	2010	Hong Z	BRAIN	DJ-1 and alpha-synuclein in human cerebrospinal fluid as biomarkers of Parkinson's disease
25	2011	Mollenhauer B	LANCET NEUROL	α-Synuclein and tau concentrations in cerebrospinal fluid of patients presenting with parkinsonism: a cohort study
25	2011	Shi M	ANN NEUROL	Cerebrospinal fluid biomarkers for Parkinson disease diagnosis and progression
24	2013	Kang JH	JAMA NEUROL	Association of cerebrospinal fluid β-amyloid 1–42, T-tau, P-tau181, and α-synuclein levels with clinical features of drug-naive patients with early Parkinson disease
24	2014	Adler CH	NEUROLOGY	Low clinical diagnostic accuracy of early vs advanced Parkinson disease: clinicopathologic study
22	2017	Poewe W	NAT REV DIS PRIMERS	Parkinson disease
39	2019	Parnetti L	LANCET NEUROL	CSF and blood biomarkers for Parkinson's disease

activation, and cytokines, which may play a role in Parkinson's disease [28,30–32].⑤ Application of brain imaging techniques: Researchers focus on the use of brain imaging techniques such as magnetic resonance imaging, positron emission tomography, and transcranial sonography for the diagnosis and study of Parkinson's disease [33–36].

4.2. Future trends

The rise of exosomes and plasma biomarker research has become a research hotspot, as they play important roles in biomarker research for Parkinson's disease (PD). Additionally, exosome research is closely linked to PD and plasma biomarkers.②Research on miRNA is closely related to PD and has the potential to play a role in elucidating the pathological mechanisms and biomarker discovery of PD, and is also associated with research on Alzheimer's disease.③Cerebrospinal fluid plays a crucial role in biomarker research for PD, and future studies will focus on the biomarkers in cerebrospinal fluid and explore their applications in early diagnosis and disease progression monitoring of PD.④The application of machine learning in PD research is receiving increasing attention, especially in the discovery and diagnosis of biomarkers. By analyzing clinical and biological data, machine learning algorithms can assist in

differentiating between PD patients and non-patients, predicting disease outcomes and treatment responses. ⑤nimal models of PD play a crucial role in research, and future studies will continue to delve deeper into PD animal models to better understand the disease mechanisms and identify biomarkers. These research hotspots and future trends will drive the research and application development of PD biomarkers, contributing to improved early diagnosis and treatment outcomes for PD.

5. Discussion

Parkinson's disease (PD) biomarker research has undergone significant development in recent years, with three distinct stages identified: exploration, biomarker identification, and multi-modal biomarker research. This study summarizes the current status of PD biomarker research and explores the hotspots and future trends in this field.

In terms of publications, the journal "MOVEMENT DISORDERS" stands out as the most prolific, with the highest publication count and total citation count. "ACS NANO" emerges as a journal with the highest average citations per paper. Additionally, "NPJ PARKINSON'S DISEASE," "BRAIN SCIENCES," and "AGEING RESEARCH REVIEWS" are emerging journals that have made significant contributions in the field of PD biomarkers in recent years. Author analysis reveals that Mollenhauer, Brit has contributed the highest number of papers, while Salem, Sultan A. has the highest average citations per paper. Mollenhauer, Brit, Frasier, Mark, and Zhang, Jin serve as core authors in the PD biomarker field. New and notable authors include Foroud, Tatiana, Lingor, Paul, and Siderowf, Andrew. In terms of countries/regions, the United States leads in national collaboration networks, publication count, and total citation count. USA, Germany, China, and Italy were the core countries in this field, showcasing their research achievements. Among institutions, the University of Pennsylvania stands out with the largest collaboration network and publication count. University College London (UCL), capital med univ, and univ med ctr gottingen also demonstrate significant contributions. Neurosciences emerge as the most important research direction within the included literature, reflecting the emphasis on understanding the neurological aspects of PD biomarkers.

Keyword analysis highlights the prominence of terms such as Parkinson's disease, Alzheimer's disease, cerebrospinal fluid, and alpha-synuclein. PD biomarkers are classified into five categories: α-synuclein-related markers, neurotransmitter-related markers, inflammation and immune system-related markers, oxidative stress and mitochondrial function-related markers, and brain imaging-related markers. The co-cited article analysis identifies major domains of PD biomarkers, including "dj-1," "extracellular vesicles," "molecular imaging," and "cerebrospinal fluid.,"

Research hotspots in PD biomarker research include α-synuclein-related markers, neurotransmitter-related markers, oxidative stress, mitochondrial function, the immune system, inflammation, and the application of brain imaging techniques. Future trends focus on exosome and plasma biomarker research, miRNA studies, cerebrospinal fluid as a crucial biomarker source, the application of machine learning, and continued advancements in PD animal models.

6. Limitations

1. Search strategy limitations: This study used the world's largest and internationally recognized Web of Science database as the source of literature, obtaining a specific set of 643 articles. Despite our efforts to select relevant articles, it is still possible that some articles may have been overlooked. For example, publications on MRI and PET/SPECT techniques as potential biomarkers for Parkinson's disease may have been overlooked because they did not contain the search keywords. Future research suggests including more databases to ensure a more comprehensive collection of articles. Secondly, employing manual searching and citation tracking methods to identify relevant research papers that may not have been automatically retrieved.
2. Interpretation Bias: The interpretation of the analysis relies on the expertise and subjective judgment of the researcher. Different researchers may have different interpretations or emphasize different aspects of the findings. Therefore, the interpretation of the results should be approached with caution.
3. Time limitation: This study analyzed and summarized literature from a specific time period. Considering that citation counts require time to accumulate, the number of citations for recently published literature is relatively low. Therefore, this paper may not fully reflect the latest trends and developments in the field of PD biomarker research.

7. Recommendations for clinicians

In light of the latest trends and findings in PD biomarker research, we offer the following recommendations for clinicians:

Strengthen research on early diagnosis of PD: Early diagnosis is crucial for the treatment and management of PD. Based on the latest research advancements, we recommend using specific protein biomarkers in blood or cerebrospinal fluid, such as α-synuclein and exosomes, as early diagnostic tools. These biomarkers include α-synuclein and exosomes, among others.

Advancements in multimodal biomarker research: Future studies should focus on combining various biomarkers to improve the accuracy of PD diagnosis and disease assessment. Researchers can perform comprehensive analyses by integrating protein biomarkers with metabolic products, imaging markers, and other factors to obtain more accurate diagnostic results.

Application of personalized medicine: Understanding individual differences in PD patients is crucial for treatment and management. We suggest that clinical doctors introduce genetic sequencing, metabolic status, and other biological indicators, under permissible conditions, to develop targeted treatment plans and monitoring methods.

Multicenter large sample studies: Although many PD biomarkers have been proposed, there is still a lack of multi-center large-sample clinical research. Doctors are encouraged to participate in international academic exchanges, collaborate with other research teams, to provide more reliable data support for the establishment and validation of biomarkers, in order to maximize the accuracy and

effectiveness of diagnosis and treatment.

Promoting the application of machine learning and artificial intelligence: Machine learning and AI technologies hold great potential for PD biomarker research. These technologies can assist in analyzing large amounts of complex data to uncover hidden patterns and correlations. Physicians can actively adopt these technologies in clinical practice to provide more accurate and personalized diagnosis, monitoring, and treatment.

Funding

The National Natural Science Fund of China provided funding for this study (No. 82174491).

Additional information

No additional information is available for this paper.

Data availability statement

Data will be made available on request.

CRediT authorship contribution statement

Xingxin Wang: Writing – original draft, Visualization, Conceptualization. **Tiantian Dong:** Software, Data curation. **Xuhao Li:** Software, Data curation. **Wenyan Yu:** Software, Methodology. **Zhixia Jia:** Software, Data curation. **Yuanxiang Liu:** Writing – review & editing, Supervision. **Jiguo Yang:** Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The authors express their gratitude for the utilization of Microsoft Excel, CiteSpace,V.6.1.R6, VOSviewer 1.6.18, and Scimago Graphica 1.0.35 software tools in this study.

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