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# Quantitative analysis of literature on diagnostic biomarkers of Schizophrenia: revealing research hotspots and future prospects

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## Abstract

**Background** Schizophrenia (SCZ) is a complex mental disorder characterized by a wide range of symptoms and cognitive impairments. The search for reliable biomarkers for SCZ has gained increasing attention in recent years, as they hold the potential to improve early diagnosis and intervention strategies. To understand the research trends and collaborations in this field, a comprehensive Bibliometric analysis of SCZ and biomarkers research was conducted.

**Methods** A systematic search of the Web of Science Core Collection was performed to retrieve relevant articles published from January 2000 to July 2023. The search focused on SCZ and biomarkers. Bibliometric tools, including CiteSpace, VOSviewer, and R package Bibliometrix, were utilized to perform data extraction, quantitative analysis, and visualization.

**Results** The search focused on SCZ and biomarkers, and a total of 2935 articles were included in the analysis. The analysis revealed a gradual increase in the number of publications related to SCZ and biomarkers over the years, indicating a growing research focus in this area. Collaboration and research activity were found to be concentrated in the United States and Western European countries. Among the top ten most active journals, "Schizophrenia Research" emerged as the journal with the highest number of publications and citations related to SCZ and biomarkers. Recent studies published in this journal have highlighted the potential use of facial expressions as a diagnostic biomarker for SCZ, suggesting that facial expression analysis using big data may hold promise for future diagnosis and interventions. Furthermore, the analysis of key research keywords identified inflammatory factors, DNA methylation changes, and glutamate alterations as potential biomarkers for SCZ diagnosis.

**Conclusion** This Bibliometric analysis provides valuable insights into the current state of research on SCZ and biomarkers. The identification of reliable biomarkers for SCZ could have significant implications for early diagnosis and interventions, potentially leading to improved outcomes for individuals affected by this challenging mental disorder. Further research and collaborations in this field are encouraged to advance our understanding of SCZ and enhance diagnostic and therapeutic approaches.

**Keywords** SCZ, Biomarkers, Bibliometrics, VOSviewer, CiteSpace

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## Introduction

Schizophrenia (SCZ) is a complex mental disorder that has long been a focal point of medical research. Its clinical manifestations are diverse, including hallucinations, delusions, emotional blunting, and cognitive impairments [1]. Despite the rich clinical experience in diagnosing SCZ, the diagnostic process remains challenging due to its complex etiology and diverse symptomatology.

Biomarkers are indicators that can be measured, and these measurements can serve as quantifiable data for normal biological processes, pathological processes, or responses to exposure or interventions. They aid doctors in better diagnosing and determining the disease and its response to interventions [2]. In recent years, with advancements in biology and neuroimaging, research on biological biomarkers for SCZ has garnered increasing attention [3]. Early diagnosis and individualized treatment are crucial for improving patient outcomes [4–7]. Numerous studies have shown that SCZ patients exhibit abnormalities in inflammatory factors, DNA methylation changes, and reduced glutamatergic function. For example, elevated levels of inflammatory factors like IL-6 in SCZ patients can aid in early diagnosis and predict disease progression and treatment response [8–10]. Neuroimaging technologies like MRI and fMRI also play an important role in revealing structural and functional abnormalities in the brains of SCZ patients. Nina V. Kraguljac et al. conducted a review on the use of neuroimaging as biomarkers for SCZ. Ideally, biomarker development targets should reflect fundamental neurobiological changes, have analogs in preclinical models, correlate with clinical symptom severity, and align with disease pathology models. In terms of genetic analysis, genome-wide association studies (GWAS) have identified gene variants related to SCZ, such as NRXN1, APBA2, NRG1, and CNTNAP2, which play key roles in synaptic development and neurotransmission [11]. In their review, Kraguljac et al. examined several potential biomarker targets related to SCZ, including dopamine hyperactivity, NMDA receptor hypofunction, hippocampal hyperactivity, neuroinflammation/immune dysregulation, connectivity issues, and cortical gray matter loss. These biomarkers are closely associated with SCZ symptomatology, symptom severity, and treatment response [6]. Simultaneously, Astafeva analyzed peripheral blood mononuclear cells in SCZ to identify related biomarkers, including changes in pro-inflammatory and anti-inflammatory markers, proteins, receptors, enzyme activities, and gene expressions as potential biomarkers [12].

Bibliometrics is a quantitative research method that involves statistical analysis of published literature to reveal research hotspots and trends in a field [13, 14]. By using bibliometric techniques, one can systematically analyze the development trends, geographical distribution of research, institutions, and journals contributing the most to a specific area, while also gaining insights into the research hotspots and frontiers within that field [15].

In this study, we employed Bibliometric software such as Bibliometrix, citespace, Vosviewer, along with R language, to investigate the literature on biomarkers for the diagnosis of SCZ. This comprehensive analysis aims to gain a deeper understanding of the potential value of biomarkers in diagnosing SCZ [16–18]. Our goal is to systematically analyze the research progress in the field of diagnostic biomarkers for schizophrenia through bibliometric methods, aiming to uncover research trends and hotspots. Specifically, we will examine publication volume, major research institutions, patterns of international collaboration, and high-frequency keywords and co-citation networks to identify key biomarkers and emerging trends in the diagnosis of schizophrenia. Through this analysis, we hope to provide strong support for the early diagnosis and personalized treatment of schizophrenia, offering guidance for future research directions. Ultimately, this study aims to advance the development of this field and improve patient prognosis.

## Data and methods

### Literature retrieval and selection

We conducted a bibliometric analysis using the Web of Science database, which offers significant advantages for bibliometric research compared to other databases. Firstly, Web of Science covers a broader range of disciplines. Secondly, it has a long temporal span and includes various data types. Most importantly, Web of Science provides powerful citation analysis tools that are crucial for detailed citation, trend, and impact analyses. Our literature retrieval process was as follows: 1. Define search terms: We used "biomarker*" and "schizophren*" as our search terms, with the search query TS = (biomarker*) AND TS = (schizophren*) (TS indicates topic). 2. Advanced search: We conducted our search using the advanced search function of the Web of Science database. 3. Inclusion and exclusion criteria: Inclusion criteria: (1) Articles published between 2000 and 2023; (2) Articles written in English; (3) Articles categorized as reviews and research papers. Exclusion criteria: (1) Studies unrelated to SCZ or biomarkers; (2) Non-academic articles such as conference abstracts, book reviews, editorials, etc.; (3) Duplicate publications.

### Bibliometric and visualization analysis

In this study, we employed a range of bibliometric tools for data extraction and analysis, including the bibliometrix package in R, CiteSpace, and VOSviewer. These tools

were selected for their respective capabilities: bibliometrix offers robust bibliometric analysis features, enabling the calculation of indicators such as the number of publications, authors, and citations, and the generation of time trend graphs and author collaboration networks, which facilitate a comprehensive understanding of research trends and hotspots [19]. CiteSpace is a visualization tool designed to uncover the interconnections between keywords and authors in the literature, displaying topic clusters and knowledge structures. By producing time graphs, co-citation networks, and keyword co-occurrence analyses, CiteSpace elucidates relationships between articles and identifies research frontiers and interdisciplinary domains [16, 20]. VOSviewer is utilized for clustering and visualization analysis, enabling the classification of publications into distinct topic groups and generating visualizations that depict the distribution of research topics. Through co-citation analysis, keyword co-occurrence analysis, and clustering diagrams, VOSviewer's visualization capabilities help identify research hotspots and key publications [21]. Additionally, we integrated the ggplot2 package to further enhance the visualization of the analysis results [22, 23].

The specific steps for data extraction and analysis began with the exportation of qualified literature data from the Web of Science database, selecting text files containing fields such as article title, author, publication year, journal name, keywords, abstract, and citation counts. The bibliometrix package was then used to import the Web of Science data, calculate key metrics such as the number of publications, authors, and citations, and generate time trend graphs and author collaboration networks, in addition to producing detailed statistical charts. In the subsequent CiteSpace and VOSviewer analyses, VOSviewer was used to parse and process the literature data, including co-citation analysis (such as author co-citation and literature co-citation) and keyword co-occurrence analysis, revealing the relationships between the literature and the research frontier. VOSviewer performed cluster analysis of publications by setting the analysis type to literature co-citation or keyword co-occurrence, selecting appropriate clustering algorithms and thresholds, and generating cluster diagrams to identify research hotspots and key topics. CiteSpace was employed for trend analysis to investigate the evolution of literature over time, identify the development trajectories and shifts in research topics, and generate emergent detection to uncover how research hotspots in significant fields have evolved. CiteSpace's trend analysis function also identifies high-frequency keywords, cutting-edge research, and influential cited literature within specific time periods, aiding in the understanding of dynamic shifts in the research field and helping to predict future research directions. Finally, the ggplot2 package was utilized to further visualize the analysis results, providing clearer representations of research trends and hotspots.

## Results

### Search results

After excluding non-English articles and those not categorized as reviews or research papers, the search results indicated that the Web of Science database contained a total of 2,935 articles from January 2000 to July 2023. Among these, there were 2,247 research papers and 601 review articles. Before 2005, the number of publications remained in the single digits. However, since then, the number of publications has shown an increasing trend each year, despite a slight decline in 2017. From 2017 onwards, the number of publications on diagnostic biomarkers for SCZ has consistently increased. By 2022, the number of articles related to SCZ diagnostic biomarkers reached 422, as shown in Fig. 1.

### Distribution characteristics of literature

Among 84 countries and regions, the United States ranked first in the number of publications with 721 articles (29.03%), followed by China with 487 articles (19.06%), and the United Kingdom with 198 articles (5.13%). The United States had the highest rate of multiple country collaborations (MCP) at 46.9%, indicating close international cooperation (Table 1). Among the 3,670 institutions, the top three with the most publications are the University of California System (354 papers), Harvard University (282 papers), and the University of London (261 papers) (Fig. 2A). Among the 708 included journals, the top ten journals published a total of 770 papers (26.24%), with the highest number of publications in the journal "Schizophrenia Research" (156 articles) (Fig. 2B). The journal with the highest total citations among the published articles was "Schizophrenia Research" with a total of 9,428 citations (Fig. 2C). There were a total of 14,151 authors included, with the top five authors being Bahn S (47 articles), Calhoun VD (47 articles), Guest PC (41 articles), Pearlson GD (33 articles), and Maes M (31 articles), collectively contributing to 199 articles (6.78%) (Fig. 2D).

### Co-citation analysis

Global citations and local citations are two important concepts in bibliometrics. Global citations refer to the number of times a particular document is cited within the entire database, measuring its citation impact across

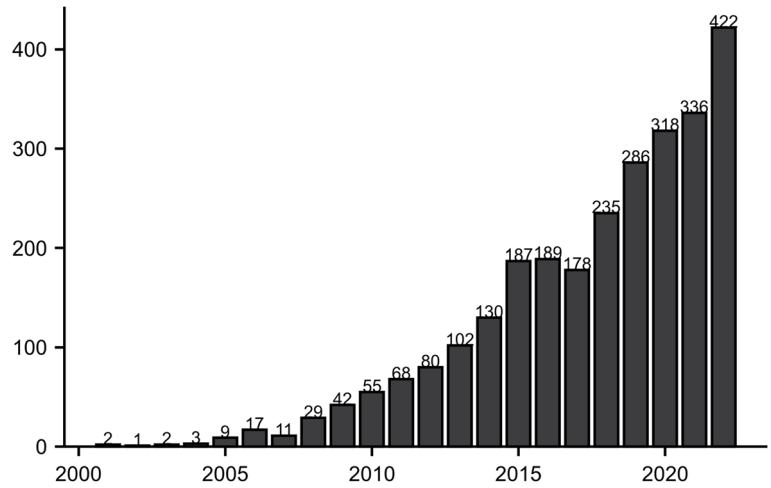


**Fig. 1** Number of annual articles on SCZ and biomarker by years

**Table 1** Top 10 countries or regions by SCZ and biomarker publication volume (2000–2023)

| Number | Country | Articles | SCP | MCP | Freq |
|---|---|---|---|---|---|
| 1 | USA | 721 | 532 | 189 | 0.246 |
| 2 | China | 487 | 344 | 143 | 0.166 |
| 3 | United Kingdom | 198 | 79 | 119 | 0.067 |
| 4 | Germany | 139 | 62 | 77 | 0.047 |
| 5 | Japan | 119 | 102 | 17 | 0.041 |
| 6 | Australia | 102 | 48 | 54 | 0.035 |
| 7 | Canada | 101 | 48 | 53 | 0.034 |
| 8 | Brazil | 99 | 51 | 48 | 0.034 |
| 9 | ITaly | 93 | 57 | 36 | 0.032 |
| 10 | SpainAA | 87 | 63 | 24 | 0.03 |

all literature. Local citations, on the other hand, indicate the number of times a document is cited within a specific subset, measuring its citation context and impact in a particular area. The proper use of these metrics can help researchers and institutions more effectively evaluate academic influence and make more informed research decisions [24, 25]. In the co-citation analysis, the most globally cited article was "Animal models of neuropsychiatric disorders" published by Eric J Nestler et al. in "Nature Neuroscience," with a total of 1,366 citations. The second most cited article was "Clinical use of current polygenic risk scores may exacerbate health disparities" published by Alicia R Martin et al. in "Nature Genetics," with a total of 954 citations. The third most cited article was "Prenatal infection and SCZ: a review of epidemiologic and translational studies" by Alan S Brown et al. in "The American Journal of Psychiatry," with a total of 879 citations. This article reveals the close relationship between prenatal infection and SCZ, highlighting some susceptibility factors that contribute to the development of SCZ. It provides insights into the etiology and pathogenesis of SCZ [26]. The rest of the top cited articles are listed in Table 2. Regarding local co-citations, the most cited article was "Identification of a biological signature for SCZ in serum" by Schwarz E in "Molecular Psychiatry," with a total of 65 citations. Using multi-omics analysis methods, the study measured serum concentrations of 181 proteins and small molecules in 250 individuals with first-episode and recent-onset SCZ 35 with severe depression, 32 with euthymic bipolar disorder, 45 with Asperger syndrome, and 280 control subjects. The study demonstrated for the first time the identification of biological features of SCZ through serum biomarkers [27]. The second most cited article was "Neurophysiological biomarkers for drug development in SCZ" by Javitt DC in "Nature Reviews Drug Discovery," with a total of 59 citations. This article reviews the latest advancements in neurophysiological techniques for measuring abnormal brain function in SCZ patients and compares it with drug-induced changes. It provides a unique opportunity for discovering transformative biomarkers in SCZ drug development [28]. The third most cited article was "Identification of distinct psychosis biotypes using brain-based biomarkers" by Clementz BA in "The American Journal of Psychiatry". This article distinguishes between different presentations of mental illness, categorizing them into three biological types (Table 3) [29].

### National and institutional collaboration analysis

Figure 3 displays cooperation between countries using a world map. More red lines indicate closer

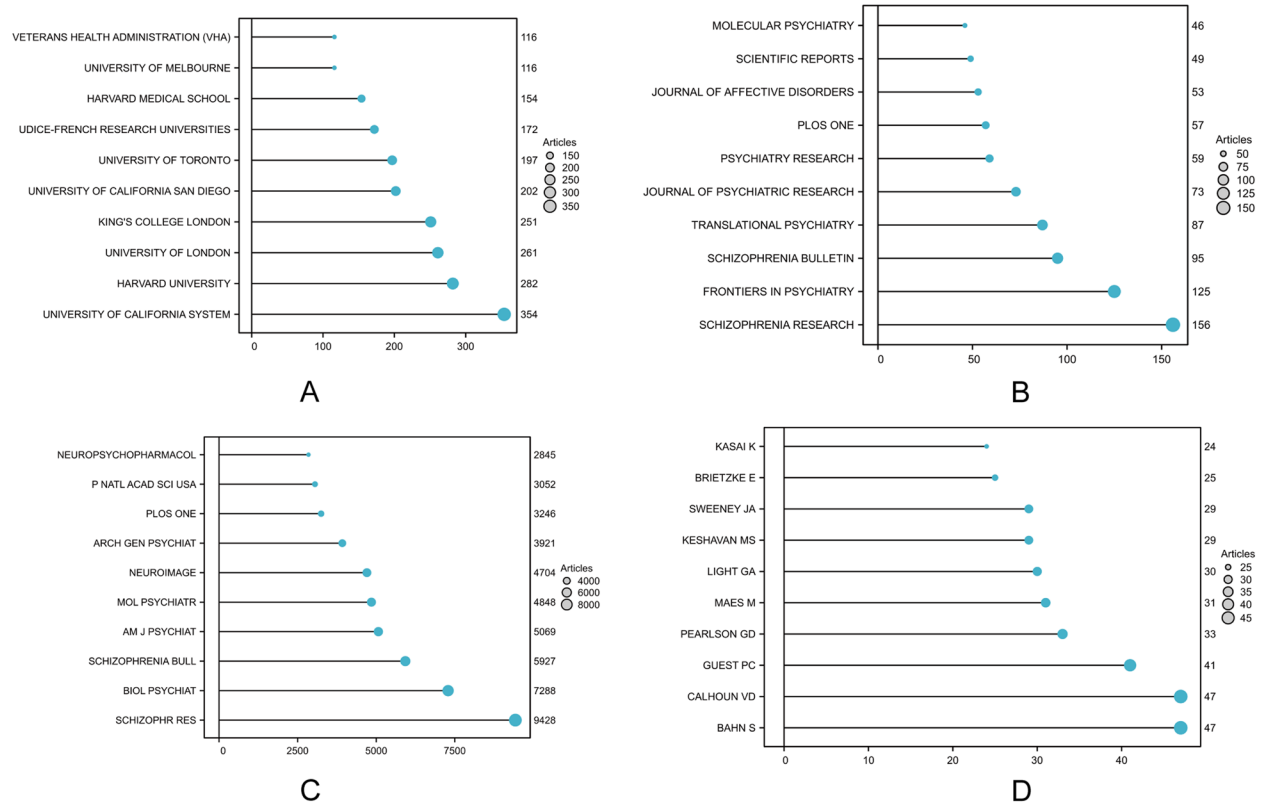


**Fig. 2** **A** Top 10 institutions with most publications in the field of SCZ and biomarker research; **B** Top 10 journals with most publications in the field of SCZ and biomarker research; **C** Top10 journals with the highest number of citations in the field of SCZ and biomarker research; **D** Top 10 authors with most publications in the field of SCZ and biomarker research

**Table 2** Top 10 articles with the highest global citations from 2000 to 2023

| Number | First Author | Article name | Journal name | Year | Global citations |
|---|---|---|---|---|---|
| 1 | Nestler EJ | Animal models of neuropsychiatric disorders | Nature Neuroscience | 2010 | 1366 |
| 2 | Martin AR | Clinical use of current polygenic risk scores may exacerbate health disparities | Nature Genetics | 2019 | 954 |
| 3 | Brown AS | Prenatal infection and schizophrenia: a review of epidemiologic and translational studies | The American Journal of Psychiatry | 2010 | 879 |
| 4 | Orrù G | Using support vector machine to identify imaging biomarkers of neurological and psychiatric disease: a critical review | Neuroscience & Biobehavioral Reviews | 2012 | 680 |
| 5 | Kapur, S | Why has it taken so long for biological psychiatry to develop clinical tests and what to do about it? | Molecular Psychiatry | 2012 | 639 |
| 6 | Fone KC | Behavioural and neurochemical effects of post-weaning social isolation in rodents-relevance to developmental neuropsychiatric disorders | Neuroscience & Biobehavioral Reviews | 2008 | 632 |
| 7 | Howes OD | Elevated striatal dopamine function linked to prodromal signs of schizophrenia | Archives of General Psychiatry | 2009 | 553 |
| 8 | He Y | Graph theoretical modeling of brain connectivity | Current Opinion in Neurology | 2010 | 514 |
| 9 | Berk M | Aspirin: a review of its neurobiological properties and therapeutic potential for mental illness | BMC Medicine | 2013 | 469 |
| 10 | Choudary PV | Altered cortical glutamatergic and GABAergic signal transmission with glial involvement in depression | P NATL ACAD SCI USA | 2005 | 466 |

**Table 3** Top 10 articles with the highest local citations from 2000 to 2023

| Number | First Author | Article Name | Journal name | Year | Local citations |
|---|---|---|---|---|---|
| 1 | Schwarz E | Identification of a biological signature for schizophrenia in serum | Molecular Psychiatry | 2012 | 65 |
| 2 | Javitt DC | Neurophysiological biomarkers for drug development in schizophrenia | Nature Review Drug Disgovery | 2008 | 59 |
| 3 | Clementz BA | Identification of distinct psychosis biotypes using brain-based biomarkers | American Journal of Psychiatry | 2016 | 56 |
| 4 | Domenici E | Plasma protein biomarkers for depression and schizophrenia by multi analyte profiling of case–control collections | PLOS ONE | 2010 | 54 |
| 5 | Orru G | Using support vector machine to identify imaging biomarkers of neurological and psychiatric disease: a critical review | Neuroscience & Biobehavioral Reviews | 2012 | 54 |
| 6 | Kapur S | Why has it taken so long for biological psychiatry to develop clinical tests and what to do about it? | Molecular Psychiatry | 2012 | 53 |
| 7 | Koutsoule ris N | Use of neuroanatomical pattern classification to identify subjects in at-risk mental states of psychosis and predict disease transition | Archives of General Psychiatry | 2009 | 52 |
| 8 | Upthegro ve R | Cytokine function in medication-naive first episode psychosis: a systematic review and meta-analysis | Schizophrenia Research | 2014 | 52 |
| 9 | Lai CY | MicroRNA expression aberration as potential peripheral blood biomarkers for schizophrenia | PLOS ONE | 2011 | 50 |
| 10 | Mondelli V | Cortisol and inflammatory biomarkers predict poor treatment response in first episode psychosis | Schizophrenia Bull | 2015 | 49 |

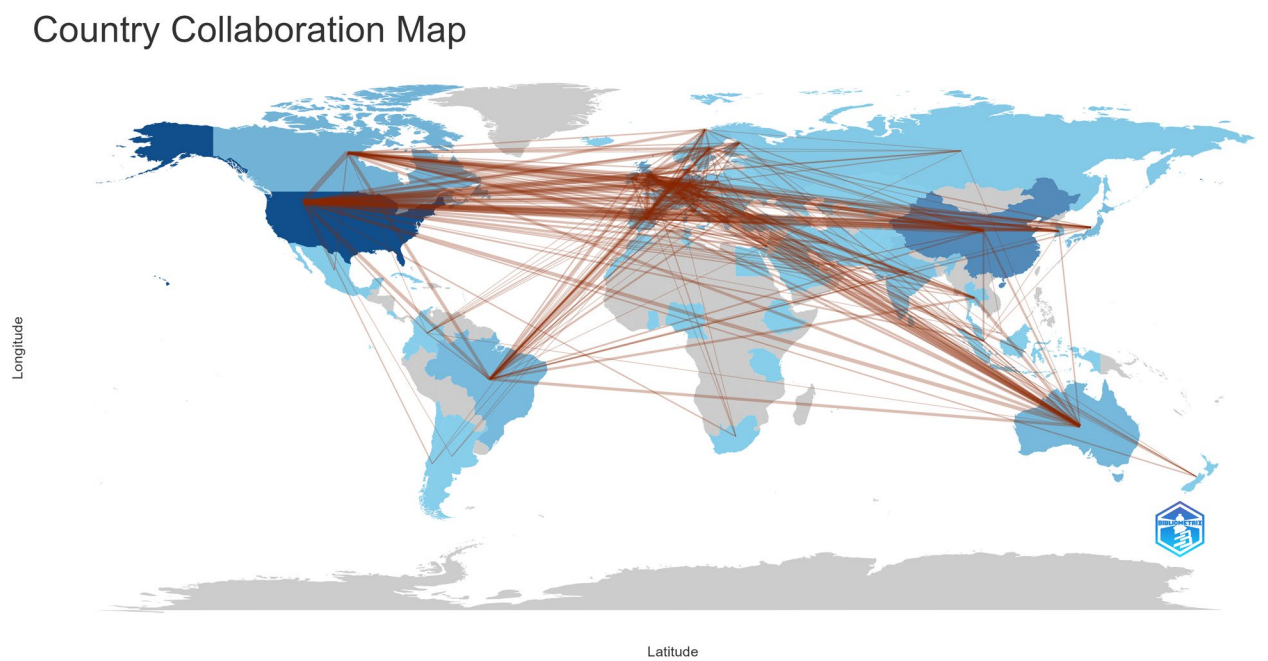


**Fig. 3** The collaboration between countries and regions on nutrition research related to sarcopenia. The colour segmentation includes blue (with publications) and grey (without publications). The thickness of the red lines indicates the number of co-published papers. The colour intensity corresponds to the number of publications)

cooperation between countries. The closest collaborations were observed between the United States and China (frequency = 150), followed by the United States and Germany (frequency = 101), the United States and the United Kingdom (frequency = 101), the United Kingdom and Germany (frequency = 97), the United States and Canada (frequency = 94), and the United Kingdom and the Netherlands (frequency = 71). This indicates that research on biological biomarkers of SCZ has exhibited a trend of globalization (Fig. 3).

### Keyword analysis and co-occurrence map

Word cloud and pie charts provide a visual representation of the distribution of keywords, highlighting the most frequently occurring ones. To gain a quick and intuitive understanding of the prominent keywords in the field of medical image segmentation, word cloud and pie charts were generated based on extracted author keywords. In Bibliometrix, "KeyWords Plus" was selected, yielding a total of 10,746 keywords. The top ten keywords, ranked in order of frequency, were as follows:SCZ (frequency = 2060, 17%), biomarkers (frequency = 590, 5%), bipolar disorder (frequency = 549, 5%), brain (frequency = 497, 4%), meta-analysis (frequency = 366, 3%), association (frequency = 350, 3%), expression (frequency = 315, 3%), prefrontal cortex (frequency = 308, 3%), risk (frequency = 294, 2%), and depression (frequency = 286, 2%). Figure 4A displays the pie chart of these keywords. For co-occurrence analysis of keywords, Using VOSviewer software with "All keywords" and "Full counting" settings, we identified 124 keywords meeting a minimum occurrence threshold of 40, aside from commonly used terms like "schizophrenia" and "biomarkers." These keywords clustered into four categories represented by colors: green, red, blue, and yellow. Cluster 1 (green) primarily focuses on biological research such as gene expression, genetics, and proteomics, including genome-wide association studies, gene expression, and epigenetics. Cluster 2 (red) relates to cognitive and brain function studies, covering topics like cognition, functional connectivity, and abnormalities. Cluster 3 (blue) is associated with inflammation, oxidative stress, and psychosis themes, indicating research into these areas' relevance to SCZ. Cluster 4 (yellow) involves neurodegenerative diseases like Alzheimer's and Parkinson's, distinct from SCZ.

Additionally, using Bibliometrix's "Co-occurrence Networks" option, we mapped these clusters in three colors: red, green, and blue. Central nodes included "Schizophrenia" and "Biomarkers." The blue area mainly concerns clinical and diagnostic research on SCZ symptoms, disease progression, diagnosis, and brain function, closely linked with biomarkers, emphasizing their importance in understanding and diagnosing SCZ. The green area is primarily associated with molecular biology and genetics research, highlighting their role in identifying and understanding SCZ biomarkers through gene expression, genome-wide association studies, oxidative stress, and inflammation.The red area focuses on cognitive function and brain imaging studies related to SCZ, including functional connectivity, working memory, and cognitive deficits. These studies contribute to understanding cognitive impairments and brain function abnormalities in SCZ patients. This visualization provides insights into current research hotspots in the field of medical imaging segmentation. Figure 4D shows the top 20 keywords with the strongest citation bursts from 2013 to 2023. Notably, keywords such as "cognitive impairment" (2021–2023), "white matter" (2021–2023), and "diagnosis" (2021–2023) have received considerable attention in recent years, indicating potential areas of future research focus.These analyses offer valuable insights into the current state of research and the emerging trends in the study of diagnostic biomarkers for SCZ.

## Discussion

SCZ is a complex mental disorder with intricate pathophysiological mechanisms. However, with the development of imaging and omics technologies, the number of studies on SCZ biomarkers has gradually increased. This study aims to explore the research trends of SCZ biomarkers to provide directions for future research. From the perspective of publication volume, this field has experienced significant growth since 2000, especially showing a continuous upward trend after 2017, indicating increasing research interest and recognition, making it an emerging hotspot [30]. In terms of publications by country and region, the United States has the highest number of publications and the most collaborations with other countries or regions. Although China has the second-highest number of publications, it has a lower frequency of cooperation with other countries, similar to results in other research fields [31, 32]. Academic development is closely related to a country's economic strength and the level of government support for the healthcare field [33], Data shows that the United States invests more in healthcare, resulting in more research outputs [34–36].

Keywords are very important in scientific research, reflecting the core themes of a research field. The frequency and co-occurrence of keywords are essential parts of bibliometric analysis. Keyword clustering analysis found that the research mainly revolves around SCZ and biomarkers, including cognition, oxidative stress, inflammation, genetics, and brain imaging studies. Early studies focused on neurotransmitter imbalances and brain structural abnormalities, later developing into network biomarker research. In recent years, the development of genomics technology has found that SCZ is closely related to genetic factors, with structural or copy number variations in synapse-related genes in the chromosomes of SCZ patients. Meanwhile, inflammatory factors, oxidative stress markers, and neurotransmitter metabolites in SCZ patients have also gradually attracted attention. Current research suggests that immune inflammation is one of the causes of SCZ, with elevated levels of cytokines such as IL-6 in the serum of SCZ patients [37]. Analysis of protein–protein


D **Top 20 Keywords with the Strongest Citation Bursts**

| Keywords | Year | Strength | Begin | End | 2013 - 2023 |
|---|---|---|---|---|---|
| prepulse inhibition | 2013 | 8.81 | **2013** | 2015 | |
| serum | 2013 | 6.54 | **2013** | 2015 | |
| anterior cingulate cortex | 2013 | 6.18 | **2013** | 2016 | |
| dorsolateral prefrontal cortex | 2013 | 5.74 | **2013** | 2016 | |
| major depression | 2013 | 5.61 | **2013** | 2016 | |
| mass spectrometry | 2014 | 9.66 | **2014** | 2016 | |
| schizophrenia patients | 2014 | 5.79 | **2014** | 2016 | |
| dysregulation | 2014 | 5.59 | **2014** | 2015 | |
| antipsychotic treatment | 2016 | 10.53 | **2016** | 2018 | |
| ultra high risk | 2013 | 11.11 | **2017** | 2020 | |
| performance | 2014 | 7 | **2017** | 2018 | |
| fmri | 2017 | 6.44 | **2017** | 2019 | |
| 1st episode schizophrenia | 2015 | 5.72 | **2017** | 2020 | |
| clinical high risk | 2017 | 12.28 | **2019** | 2020 | |
| treatment response | 2019 | 7.77 | **2019** | 2021 | |
| blood | 2014 | 7.19 | **2019** | 2021 | |
| network | 2018 | 9.69 | **2020** | 2023 | |
| diagnosis | 2017 | 10.69 | **2021** | 2023 | |
| cognitive impairment | 2013 | 6.26 | **2021** | 2023 | |
| white matter | 2018 | 5.68 | **2021** | 2023 | |

**Fig. 4** **A** Dendrogram of the top 50 keywords for articles in the field of SCZ and biomarker research; **B** Keyword co-occurrence cluster plot for SCZ and biomarker research articles from 2000 to 2023 by VOSviewer; **C** Keyword co-occurrence cluster plot for SCZ and biomarker research articles from 2000 to 2023 by Bibliometrix; **D** Visualization map of top 20 keywords with the strongest citations bursts in the field of SCZ and biomarker research

interaction networks in the brain tissue of SCZ patients shows abnormalities in several immune-related pathways, including interleukin and natural killer cell signaling, NF-kB signaling, and B cell receptor signaling, all related to immune function and inflammatio. Therefore, changes in inflammation markers and gene expression may become potential diagnostic biomarkers for SCZ in the future [35, 36, 38].

Understanding research hotspots is crucial for researchers as it helps them grasp the current trends in the field. In SCZ and diagnostic biomarker research, our study identified major research directions, including elucidating potential diagnostic biomarkers for SCZ and the intricate relationships between SCZ and other psychiatric disorders. Utilizing gene testing and measuring substances like inflammatory markers in the blood could assist in identifying potential diagnostic biomarkers for SCZ and distinguishing it from conditions like depression, Alzheimer's, and bipolar disorder, leading to improved diagnosis [3, 39–43].

The citation analysis of articles reflects their academic impact. Among the top ten globally cited and locally cited articles in this study, the focus was primarily on exploring the relationship between SCZ and plasma biomarkers. Clinically, psychiatrists rely mainly on patients' clinical presentations, such as positive symptoms like hallucinations and delusions, and negative symptoms like social withdrawal, for diagnosing SCZ [44]. However, diagnosing solely based on clinical experience may carry the risk of misdiagnosis [45]. Early biological biomarkers play a critical role in diagnosing SCZ, as early diagnosis and treatment can alleviate symptoms and lead to better clinical outcomes [46]. Extensive research has revealed that individuals with SCZ exhibit abnormalities in inflammatory factors, DNA methylation alterations, and reduced glutamatergic function. Despite the current challenges in SCZ biomarker research due to the limitations of sample size, population diversity, and diagnostic variability, which complicate the validation and replication of research findings, the changes observed in the SCZ population remain worth further investigation and verification (McCarroll et al., 2014). Notably, the elevation of the inflammatory factor IL-6 has been observed in SCZ patients, with multiple studies indicating increased IL-6 levels in both first-episode SCZ patients and those who have undergone treatment [37, 47, 48]. These alterations hold potential as prospective diagnostic biomarkers for SCZ in the future [5, 49, 50].

In the field of SCZ research, burst detection analysis has highlighted the evolution of research hotspots in recent years, particularly in the areas of diagnosis, biomarkers, and alterations in white matter. Since 2021, the citation frequency of these keywords has surged, indicating a growing focus on these topics within the scientific community. Several key trends in SCZ research have emerged:

The role of biomarkers in the diagnosis of SCZ has become a prominent research direction. Researchers are actively working to identify hematologic molecular markers or imaging markers that can accurately predict and diagnose SCZ. Diana O. Perkins and colleagues, who investigated the expression of plasma analytes associated with inflammation, oxidative stress, hormones, and metabolism to predict psychiatric disorders, found that the activation and dysregulation of the immune system may play a central role in the development of psychosis. Emerging evidence linking inflammation with schizophrenia continues to accumulate, supporting this hypothesis. Furthermore, multiplex blood testing has shown significant clinical utility, particularly if validated in other high-risk populations for psychosis [51]. João E Rodrigues et al. conducted a systematic review and meta-analysis of the application of mass spectrometry proteomics in human peripheral fluids in assessing potential biomarkers of schizophrenia and found that FCN3 was upregulated and APO1, APOA2, APOC1, and APOC3 were downregulated in SCZ patients, but some confounding factors contributed to the heterogeneity of the findings [52]. Due to the complexity of schizophrenia and the diversity and uncertainty of its early symptoms, the search for biomarkers with high specificity and sensitivity is essential for early detection and intervention [53]. In the future, it is expected that more studies will focus on the development of markers combining multiomics to improve the reliability of SCZ diagnosis. 2. Abnormalities in the structure and function of the white matter are increasingly recognized as one of the core pathologies in the course of SCZ. In recent years, through the advancement of imaging technology, more and more studies have focused on the damage of white matter microstructure in SCZ patients, such as the inefficient white matter activity caused by intracerebral hemisphere and interhemisphere communication in patients with schizophrenia [54], simultaneously differences in methylation with SCZ status and tissue type were found in or near the KLF9, SFXN1, SPRED2, and ALS2CL genes [55]. In addition to dysfunction of connections between different brain regions in patients with schizophrenia, there is also an abnormal asymmetry in functional connectivity compared to healthy subjects [56]. Therefore, SCZ may not only be a neurochemical disorder, but also involves structural changes in the neural network, which further suggest that changes in our white matter may become a biomarker for SCZ diagnosis in the future,

and future studies may further explore the mechanism of white matter abnormalities and the relationship between them and clinical symptoms. Therefore, from a holistic perspective, SCZ research is gradually moving towards multi-dimensional comprehensive research, involving neuroimaging, biochemistry, biomarkers and other levels. This trend reflects the researchers' attempts to gain a deeper understanding of the pathological mechanisms of SCZ by integrating the forces of different disciplines to provide a scientific basis for personalized diagnosis and treatment. With the further advancement of technology, especially the application of big data and artificial intelligence in biomedicine, significant progress may be made in the early diagnosis and precision treatment of SCZ in the future. In summary, future SCZ research will continue to develop around diagnosis, biomarkers, changes in white matter structure, and cognitive impairment, and breakthroughs in these fields will help improve the quality of life of SCZ patients and promote scientific progress in this field [35, 36, 38].

To our knowledge, this is the first study to use bibliometric analysis to investigate SCZ and diagnostic biomarkers. Compared to traditional literature reviews, our bibliometric analysis provides a more comprehensive and intuitive overview as it combines systematic retrieval and quantitative statistical analysis. Additionally, we utilized not only CiteSpace but also VOSviewer and the R package bibliometrix for better data extraction, bibliometric analysis, and visualization. However, there are still some limitations to this study. First, we extracted only articles from the Web of Science Core Collection database, and only English articles were selected. While this option reduces the likelihood of missing literature, it also carries the risk of underrepresentation, especially for literature in other languages, which may lead to low citations or neglect of some regional research results [57]. Moreover, the use of a single database may lead to incomplete coverage of certain research areas, especially from different countries and regions, which may affect the comprehensiveness and generalizability of the results. Future research can be achieved by integrating multiple databases (e.g., PubMed, Scopus, Embase) and multilingual literature to obtain a more representative global perspective [58, 59]. Furthermore, our bibliometric analysis approach focuses primarily on quantitative information rather than full-text analysis, which may leave out some key information that exists only in the full text, such as the research author's insights into trends, opinions, or predictions of the future direction of the field. The limitations of bibliometric methods are also manifested in the insufficient analysis of the quality of the literature, which only relies on the number of citations and the co-occurrence frequency of keywords. This approach may favor older and more cited literature and ignore emerging research published in recent years. This bias may result in results that are not fully representative of current cutting-edge research trends. There is also a certain degree of subjectivity in the selection and clustering methods of keywords, which may affect the accuracy and reliability of the results. Although we try to reduce this bias through standardized processing, we can improve the objectivity of keyword selection by introducing methods such as machine learning and natural language processing in future research to more accurately reveal research hotspots and trends. We also lack an in-depth analysis of regional research trends and global collaborative networks, especially the specific contributions of different regions in the study of biomarkers of schizophrenia and the dynamics of their collaboration. Despite the dominance of the United States and Western European countries in this area, there is a lack of comprehensive analysis of the contributions and potential of other regions. In the future, we can further study the transnational and cross-regional cooperation networks, and evaluate the role and significance of global scientific research networks in promoting research in this field by analyzing the frequency and depth of international cooperation and its impact on research quality. Finally, as this study focuses primarily on quantitative analysis, we were unable to delve into the specific quality of the content of the literature and the practical implications of these trends in the study of biomarkers of schizophrenia. Future research can conduct more in-depth discussions on the specific direction and quality of research content through a combination of qualitative and quantitative methods. For example, an in-depth qualitative analysis of quantitative trends can be used to understand the motivations behind them and assess how these trends have a real impact on diagnosis and treatment in clinical translation. Looking ahead, we recommend expanding the time horizon of the study to integrate multiple databases (e.g., PubMed, Scopus, Embase, etc.) and multilingual literature to obtain more comprehensive literature analysis results. At the same time, more detailed co-occurrence analysis and dynamic keyword clustering were carried out to identify more relevant keywords and research hotspots, and further reveal the research trends and frontier fields of schizophrenia diagnostic biomarkers. Finally, by introducing advanced data mining, machine learning and natural language processing technologies, the depth and accuracy of bibliometric analysis are improved, and more comprehensive data support and scientific guidance are provided for the research of schizophrenia.

## Conclusion

Our bibliometric analysis is expected to aid researchers in understanding the research trends in SCZ and diagnostic biomarkers. The number of publications related to this field was relatively low each year at the beginning of this century, with no clear research trend. However, in recent years, the research in this area has gradually matured. In conclusion, there is a growing interest and attention in the field of diagnostic biomarkers for SCZ, and we anticipate that there will be more research efforts to further advance our knowledge in this domain in the future.

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12888-025-06644-3.

Supplementary Material 1

### Authors' contributions

L.Y Jin and L.M Wu did the bibliometrics analysis and wrote the manuscript. J. Zhang, X.W Jia, H. Zhou, S.L Jiang, P.J Jiang and Y.F Li participated in the reaserch design and manuscript writing. Y. Li supervised and revised the manuscript. All authors contributed to the article and approved the submitted version.

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### Data availability

We commit that the data and materials obtained in this study will be made available upon request, allowing other researchers to verify our research findings and engage in academic discussions.The data availability for this article is provided in the attachment. We utilized the R package and uploaded a file named 'Bibliometrix-Export-File-2023–07-21.RData,' which allows for reproducibility. Because the data of our study was taken from the YaHS cohort, access to the data was subject to their permission. It will be available from the first author on reasonable requests.

## Declarations

### Ethics approval and consent to participate

Within the scope of this literature review, the study did not directly involve actual participants, experiments, or surveys. Therefore, ethical approval or participant consent was not applicable.

### Consent for publication

Not applicable.

### Competing interests

The authors declare no competing interests.

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## Publisher's Note