EXPLORING BIOMARKERS AND EARLY DIAGNOSIS IN ALZHEIMER'S DISEASE: A BIBLIOMETRIC ANALYSIS FROM 2013 TO 2023

OLEGÁRIO, Raphael Lopes[1]

PIANEZZER, Guilherme Augusto[2]

ABSTRACT

This study conducts a thorough bibliometric analysis spanning 2013 to 2023 to explore advancements in Alzheimer's disease (AD) biomarker research. Examining scholarly literature encompassing pivotal biomarkers—beta-amyloid proteins, tau, neurofilament light chain, and advanced imaging techniques—emphasizes their significance in early diagnosis and disease progression monitoring. Unveiling emerging trends and collaborative networks, this analysis deciphers the multidimensional landscape of AD biomarker research, providing critical insights. Findings serve as a foundational guide for future research endeavors and targeted interventions in the complex realm of AD.

Keywords: neurodegenerative diseases. biomarkers. early diagnosis. beta-amyloid proteins. neuroimaging techniques

1. INTRODUCTION

The AD represents an escalating global health challenge, demanding urgent attention toward robust biomarkers for timely detection and intervention. As the predominant form of dementia, impacting over 27 million individuals worldwide and constituting 60 to 70% of reported cases, AD typically manifests with a progressive decline in episodic memory and cognitive abilities, often followed by impairments in language and visuospatial skills (SILVA *et al.*, 2019). Beyond cognitive decline, behavioral changes, including apathy, increased aggression, and persistent depression, frequently accompany the progression of the disease (KUMAR *et al.*, 2023). This intricate combination of cognitive and behavioral alterations underscores the necessity for multifaceted approaches to early identification and targeted interventions, highlighting the urgency to unravel the complexities surrounding AD for improved diagnosis and care strategies.

The diagnostic landscape of AD poses considerable challenges attributed to its diverse pathobiology, genetic predispositions, brain resilience, and resulting distinctive clinical manifestations (DUBOIS *et al.*, 2021). This complexity underscores the significance of advancements in in vivo biomarkers, revolutionizing the trajectory of AD diagnosis by

---

transitioning it from later stages of dementia to earlier phases, potentially enabling pre-symptomatic detection (PARK *et al.*, 2022). While the clinical diagnosis heavily relies on observable symptoms, the burgeoning availability and utilization of biomarkers play an increasingly vital role in differentiating between various disorders and AD phenotypes, especially in the initial phases (DUBOIS *et al.*, 2023). These biomarkers not only aid in refining diagnostic accuracy but also serve as critical tools in identifying individuals at risk of progressing to symptomatic AD, thereby offering a crucial window for targeted interventions and tailored therapeutic strategies.

This study embarks on a comprehensive review and an expansive bibliometric analysis spanning from 2013 to 2023. Its aim is to decode the intricate evolution of AD biomarkers, delving beyond quantitative measures to unravel the nuanced intricacies of insights, trends, and transformative advancements within this domain. Central to this investigation is an unyielding focus on the pivotal role of these biomarkers in early diagnosis and monitoring disease progression. Going beyond a mere scrutiny of methodologies and findings, our objective is to reveal emerging trends, methodological nuances, and paradigmatic shifts that shape the landscape of AD biomarker research.

Moreover, this endeavor transcends conventional analysis by peering into collaborative dynamics among influential authors, publication sources, and interdisciplinary networks shaping the multidimensional spectrum of AD biomarker research. By untangling these interconnected threads, our goal is to offer a holistic understanding of the evolutionary trajectory within this crucial field. This comprehensive analysis aims not only to delineate growth trends but to decipher the qualitative evolution and multifaceted collaborative efforts within AD biomarker research. The insights gleaned from this expansive exploration serve as a guiding compass for future research, propelling the formulation of targeted interventions in the relentless pursuit of untangling the complexities of this debilitating neurodegenerative disease.

2. METHODS

This study was structured to encompass a thorough bibliometric analysis. Figure 1 illustrates our focused methodology, emphasizing the significance of extracting comprehensive insights from the gathered data. Our approach prioritized a rigorous examination, highlighting the pivotal role of bibliometric analysis in driving this research (DONTHU *et al.*, 2021).
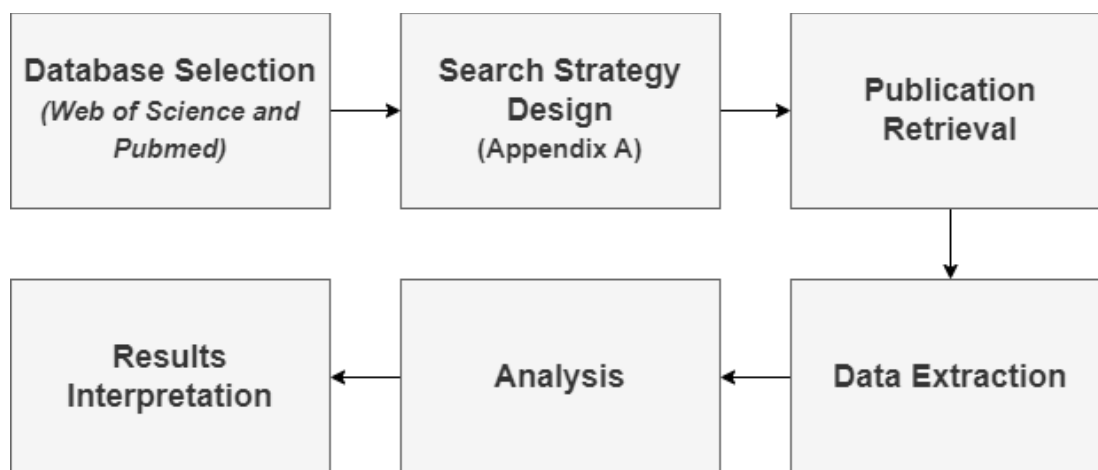
Figure 1. Visual representation of the step-by-step bibliometric analysis process.

2.1 Bibliometric Analysis

The initial phase encompassed a bibliometric investigation conducted across two electronic databases, PubMed and Web of Science. The exploration aimed to encompass a wide array of publications, including peer-reviewed articles, conference proceedings, and relevant documents published within the timeframe of 2013 to 2023, focusing specifically on biomarkers and early diagnosis in AD.

2.1.1 Search Strategy and Selection Criteria

A systematic and comprehensive search strategy was devised, leveraging a combination of controlled vocabulary terms (i.e., MeSH terms in PubMed). This approach was designed to retrieve studies pertinent to AD biomarkers and early diagnostic strategies. Publications were filtered based on language, with an emphasis on English-language documents. Furthermore, inclusion criteria were refined to concentrate exclusively on individuals up to 65 years old diagnosed with probable AD. This stringent criterion was employed to facilitate a concentrated analysis within this demographic cohort, essential to address the study's primary objectives. For a comprehensive outline of the search strategy, please refer to Appendix A.

3. RESULTS

3.1 Overview of Bibliometric Analysis and Publications Trends

The trend analysis of publications retrieved from PubMed and Web of Science databases reveals a consistent pattern of scholarly output over the past decade (Figure 2). In

2023, PubMed yielded 148 publications, while Web of Science recorded 411, maintaining a trend of high scholarly activity. The years 2021 and 2022 also exhibited robust publication rates across both databases, with 314 and 177 publications in PubMed and 451 and 505 in Web of Science, respectively. Over the years, a gradual fluctuation in publication counts was observed, indicating a consistent interest and contribution to the field across the investigated period. The data showcases a dynamic landscape of research output, illustrating the sustained scholarly interest in the subject matter.
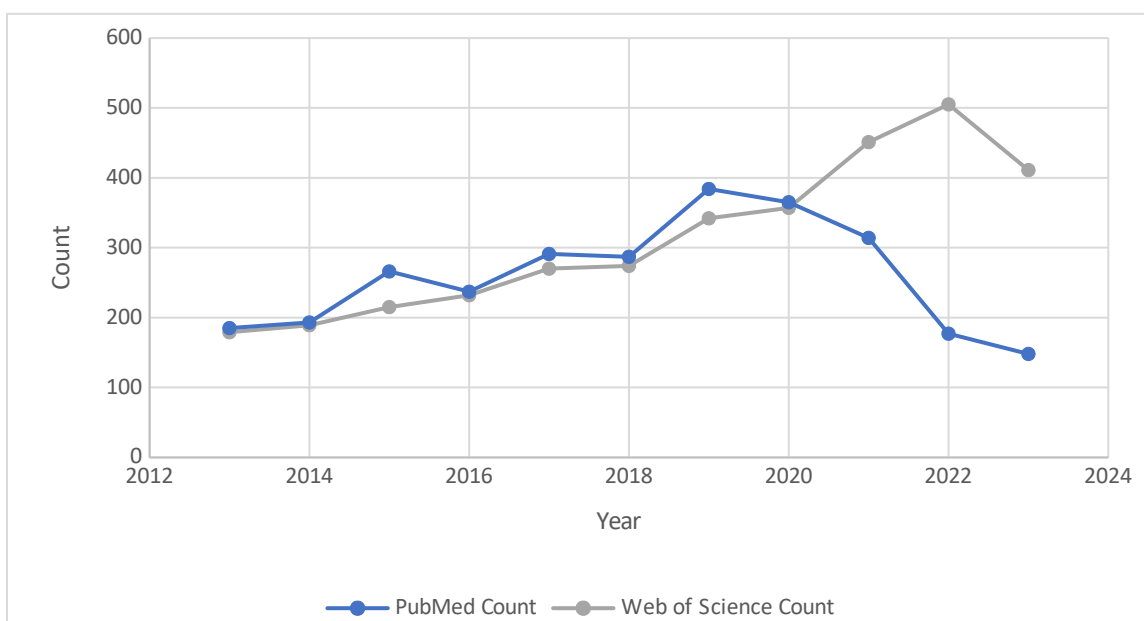
Figure 2. Publication Trends from PubMed and Web of Science Databases.

3.2 Bibliometric analysis of data within the Web of Science

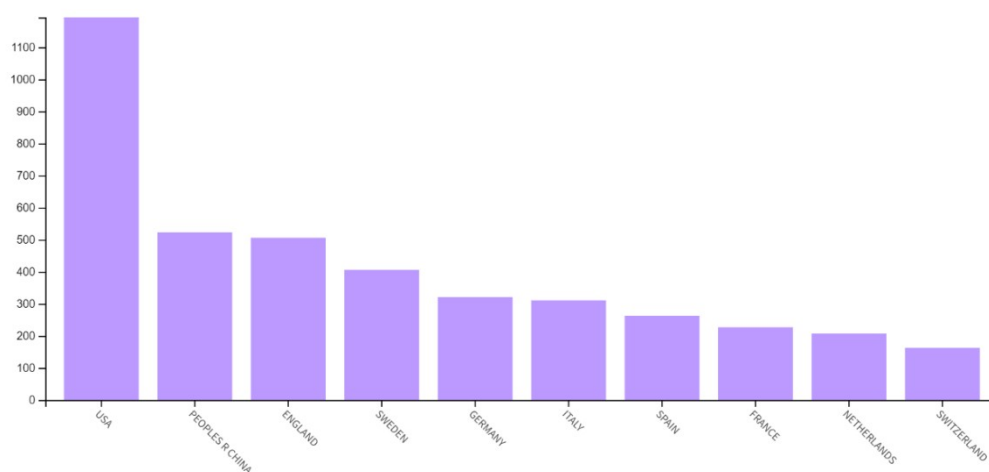### 3.2.1 Analysis of Research Areas

The Neurosciences and Neurology emerged as the most prominent research domain, constituting the highest share with 2,042 publications, accounting for approximately 59.62% of the dataset (Figure 3). Geriatrics and Gerontology followed with 359 publications, representing approximately 10.48%, while Biochemistry and Molecular Biology accounted for 286 publications, approximately 8.35% of the analyzed records. Psychiatry, Chemistry, and Science & Technology, among others, also exhibited substantial contributions to the scholarly output. The diverse spectrum of research areas underscores the multidisciplinary nature of studies contributing to this dataset, highlighting the breadth and depth of research interests across various scientific domains.

Figure 3. Research Areas Analysis Chart - Web of Science.

3.2.2 Analysis of Countries and Regions

The geographical distribution of research output showcased the dominance of several countries and regions (Figure 4). The United States led the tally with 1,193 publications, constituting approximately 34.83% of the dataset. Following closely, People's Republic of China contributed significantly with 523 publications, accounting for approximately 15.27%. England and Sweden secured substantial positions, contributing 506 (14.77%) and 406 (11.85%) publications, respectively. The analysis unveiled a diverse representation of research output across various countries and regions, signifying a global involvement in the field under study. Notably, 123 records (3.59%) did not contain data in the field being analyzed, underlining the complexity of comprehensive data retrieval in bibliometric assessments.

Figure 4. Geographical distribution of research - Web of Science.

3.2.2 Analysis of Affiliations

The study drew from a diverse array of affiliations, with the University of London leading the contributions, accounting for 9.81% of the total sample. University College London and the University of Gothenburg closely followed, representing 8.67% and 8.47% respectively (Figure 5). Notably, a range of international institutions, including the University of California System, Sahlgrenska University Hospital, and Institut National de la Sante et de la Recherche Medicale INSERM, contributed significantly, each comprising over 4% of the dataset. The collaborative nature of this research is highlighted by the substantial involvement of various institutions across different continents, signifying a global effort in the pursuit of these findings.

Figure 4. Affiliations Analysis Chart - Web of Science.

**3.2.2 Analysis of Journals**

The study encompassed a wide spectrum of publishers, with Springer Nature being the most prevalent, accounting for 16.32% of the total publications (Table 1). Elsevier closely followed at 15.85%, and Wiley contributed 13.93% of the literature surveyed. A diversity of publishers, such as IOS Press, Frontiers Media SA, and MDPI, demonstrated significant participation, each contributing over 5% of the publications. Additionally, numerous other publishers, each contributing minimally, collectively showcase the expansive landscape of publishing platforms engaged in disseminating research findings within this domain.

Table 1. Analysis of Journals - Web of Science.

| Publisher	Record Count	% of 3,425
Springer Nature	559	16.32
Elsevier	543	15.85
Wiley	477	13.93
IOS Press	429	12.53
Frontiers Media SA	212	6.19
MDPI	197	5.75
Oxford Univ Press	113	3.30
Lippincott Williams & Wilkins	82	2.39
Bentham Science Publ Ltd	65	1.90
Taylor & Francis	52	1.52

3.2.2 Analysis of Authors

The contribution of authors in this study varied, with Zetterberg H and Blennow K emerging as the most prolific contributors, accounting for 7.71% and 7.01% of the records, respectively (Figure 5). The distribution of authorship exhibited a broad spectrum of involvement, showcasing a collaborative effort among numerous researchers. Other notable contributors included Hansson O, Teunissen CE, and Molinuevo JL, each making significant contributions, highlighting the diverse range of expertise involved in this comprehensive study.
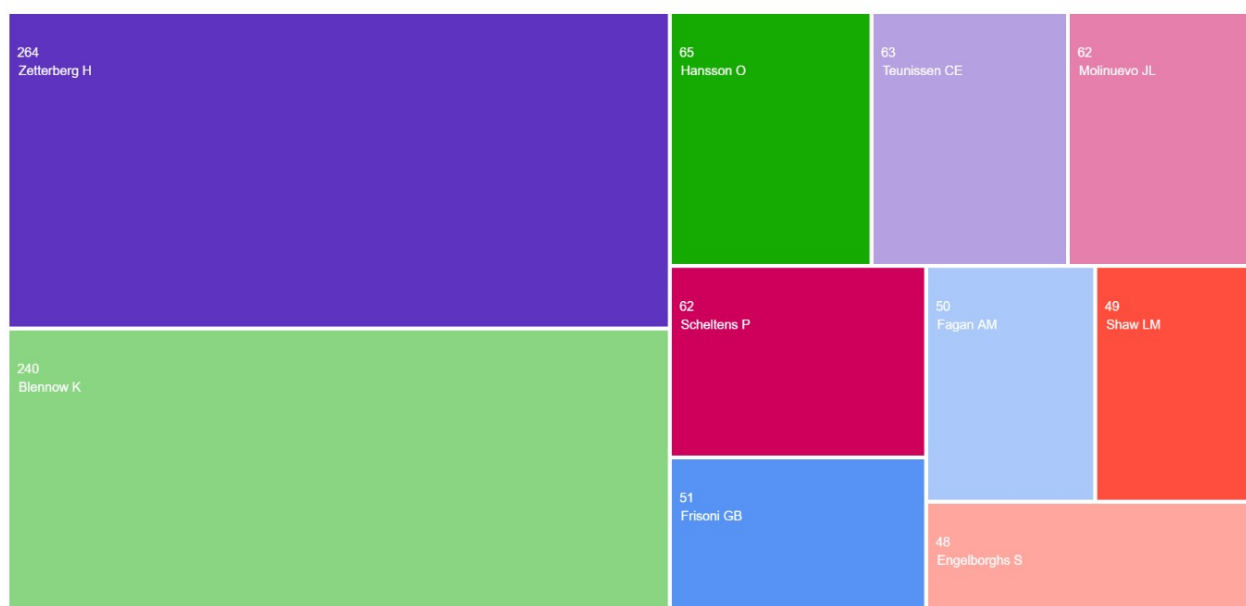
Figure 5. Analysis of Authors Analysis Chart - Web of Science.

3.3 Bibliometric analysis of data within the PubMed

3.3.1 Analysis of Keywords (Mesh-Terms) Co-Occurrence

The analysis of co-occurrence within the PubMed database using Mesh keywords revealed significant trends in research focus and interrelations between various key concepts (Figure 6). Among the most frequently occurring keywords, "aged" and "aged, 80 and over" were highly prevalent, indicating a substantial emphasis on studies concerning the elderly population. Additionally, "alzheimer disease" and associated terms like "amyloid beta-peptides," "tau proteins," and "neurodegenerative diseases" manifested considerable prominence, reflecting a robust concentration on neurodegenerative disorders. Notably, terms such as "biomarkers," "neuroimaging," and "cognitive dysfunction" indicated a multidisciplinary approach, underscoring the diverse methodologies utilized in understanding and diagnosing cognitive conditions. Furthermore, the prevalence of terms like "longitudinal studies," "prognosis," and "disease progression" suggests an emphasis on longitudinal research designs and the exploration of disease trajectories and outcomes in neurological contexts.
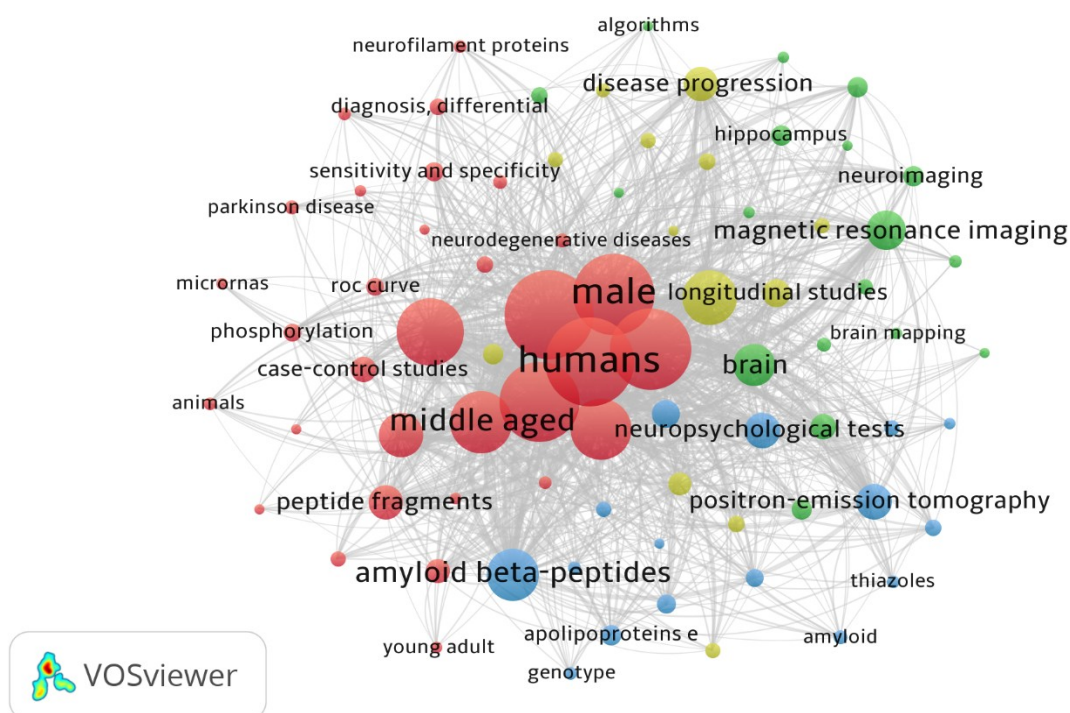
Figure 6. Analysis of Keywords Co-Occurrence – PubMed.

3.3.2 Analysis of Co-authorship

The co-authorship analysis conducted on the PubMed database unveiled crucial collaborative patterns among influential researchers (Figure 7). Notably, Kaj Blennow appeared as a central figure, contributing to 181 documents and demonstrating strong connections within the network. Henrik Zetterberg also emerged prominently, showcasing significant involvement in 190 documents, indicating substantial collaborative efforts. Sebastiaan Engelborghs, with 32 documents, reflected interconnectedness within the network. These findings highlight the collaborative landscape within this research domain, emphasizing the interconnected contributions among key authors in advancing scientific knowledge and discourse.
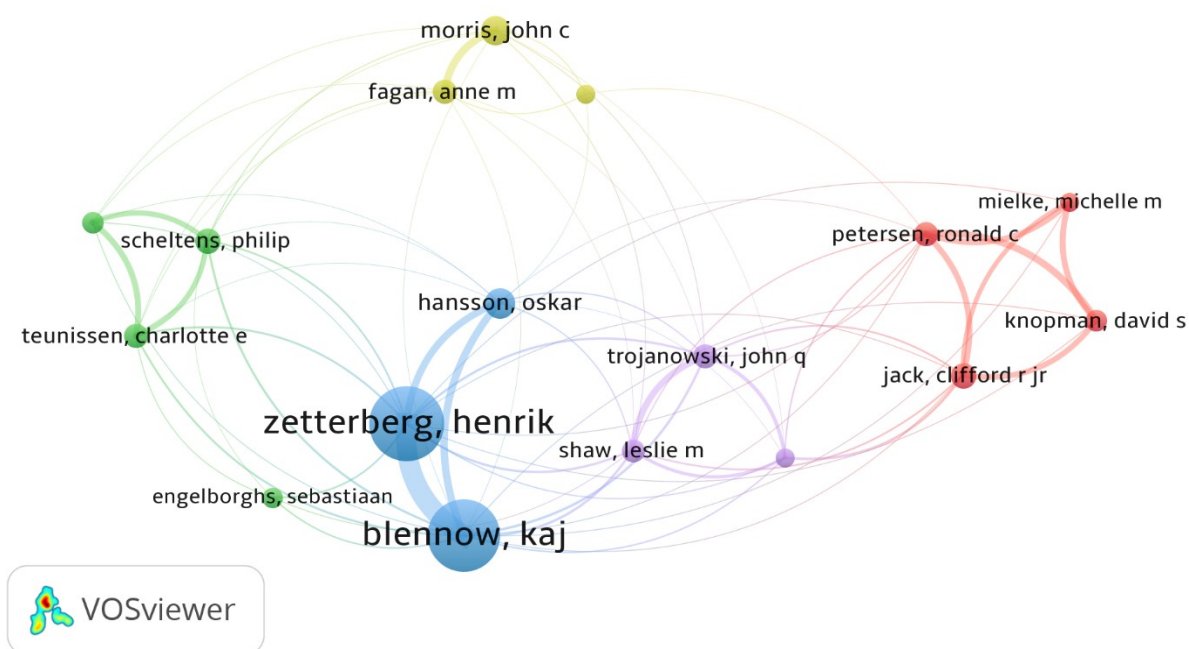
Figure 7. Analysis of Co-authorship – PubMed.

4. DISCUSSION

Throughout the bibliometric analysis encompassing data from PubMed and Web of Science, this study offered a panoramic view of scholarly activity and thematic trends in AD

biomarkers and early diagnosis. The findings unveiled a consistent trend of scholarly output over the past decade, showcasing sustained interest in this critical area of research. Specifically, 2023 witnessed 148 publications in PubMed and 411 in Web of Science, maintaining a robust trajectory. Notably, 2021 and 2022 also exhibited significant publication rates, underlining the enduring dedication and contributions made to unraveling the intricacies of Alzheimer's disease biomarkers and diagnostic strategies.

4.1 Scholarly Activity Trends in AD Research

The consistent trajectory of scholarly output witnessed over the last decade underscores the sustained interest in advancing knowledge related to AD biomarkers and early diagnosis. Notably, beyond the numerical increase, an exploration into the types of publications, such as original research articles, reviews, meta-analyses, or clinical trials, could shed light on the diverse methodologies and depth of investigations contributing to this body of knowledge. Additionally, a temporal analysis across the decade could uncover periods of increased or decreased scholarly activity, potentially correlated with pivotal breakthroughs, policy changes, or technological advancements.

4.2 Domain-specific Contributions and Global Involvement

While Neurosciences and Neurology represent the overarching categories dominating the research landscape within this domain, a more granular examination into subdomains could offer nuanced insights. Analyzing subdomains like molecular neuroscience, neuroimaging techniques, genetic studies, or clinical trials could unveil specialized areas of interest and evolving trends. Furthermore, considering geographical variations in research themes or methodologies might delineate regional preferences or strengths in AD research, providing a comprehensive understanding of global contributions.

4.3 Institutional Collaborations and Multinational Efforts

Beyond enumerating the institutions contributing significantly, a network analysis exploring collaborative patterns among these institutions might unveil the dynamics of these partnerships. Investigating the types of collaborations—whether they are interdisciplinary, intercontinental, or institutional—could illuminate the nature and extent of knowledge exchange and innovation fostered through these alliances. Moreover, examining co-authorship networks across institutions might reveal key clusters or influential groups driving collaborative research initiatives, indicating potential hubs of expertise and innovation.

4.4 Publisher Trends and Author Contributions

While Springer Nature, Elsevier, and Wiley emerge as prominent publishers, a detailed examination into their publication trends, citation rates, and impact factors might elucidate variations in publishing focus and dissemination strategies. Additionally, delving into author contributions beyond the most prolific ones could highlight the diverse spectrum of expertise driving collaborative efforts in this field. Exploring the career trajectories or multidisciplinary backgrounds of authors might provide insights into the multidimensional collaborations shaping Alzheimer's disease research.

4.5 Thematic Analysis and Collaborative Networks

Expanding the thematic analysis to encompass specific clusters of Mesh keywords or co-occurring terms might reveal interconnected themes or emerging concepts within AD research. Understanding the temporal evolution of these themes could elucidate shifts in research focus or emerging trends. Moreover, investigating collaborative networks among authors beyond the most prolific could uncover influential yet less-highlighted contributors, showcasing the breadth and diversity of expertise fueling collaborative efforts in this domain.

In essence, a comprehensive analysis across these facets within the bibliometric study offers a nuanced understanding of the multifaceted landscape of AD biomarkers and early diagnosis research. This extended analysis not only provides a broader perspective but also enables a more detailed assessment of the depth, diversity, and collaborative nature inherent in this crucial area of study.

4.6 Implications in Clinical Practice

Advancements in AD biomarker research are pivotal for effective clinical practice, addressing challenges posed by its complex pathobiology and distinct clinical manifestations. The predominant form of dementia globally, AD affects over 27 million individuals, contributing significantly to cognitive decline and behavioral changes (ALVES *et al.*, 2012). This study unravels the intricate landscape of AD biomarkers through a comprehensive bibliometric analysis spanning 2013 to 2023, emphasizing their critical role in early diagnosis and monitoring disease progression.

AD's diagnostic complexity stems from its diverse pathobiology, genetic influences, and unique clinical presentations (EDELBERG; WEI, 1996). In vivo biomarkers, a cornerstone in AD diagnosis, have shifted the diagnostic paradigm from late-stage dementia to earlier phases, enabling potential pre-symptomatic detection. While clinical diagnosis

relies on observable symptoms, biomarkers increasingly aid in differentiating between disorders and AD phenotypes, especially in initial stages, identifying individuals at risk of symptomatic AD.

This investigation delves beyond methodological scrutiny, uncovering emerging trends, methodological nuances, and paradigm shifts shaping AD biomarker research (BOMASANG-LAYNO; BRONSTHER, 2021). It explores collaborative networks among influential authors, publication sources, and interdisciplinary collaborations, offering a holistic understanding of AD's evolution. Insights derived aim not just at delineating growth trends but deciphering qualitative evolution and collaborative efforts, guiding future research and interventions.

The methodological approach encompassed a rigorous bibliometric analysis across PubMed and Web of Science, refining search strategies to include pertinent AD biomarker studies. A focused examination within a specific demographic cohort (<65 years old with probable AD) facilitated a concentrated analysis, essential to achieve primary objectives. Results highlighted sustained scholarly activity, particularly in recent years, signifying consistent interest in AD biomarkers and diagnostic strategies. Neurosciences and Neurology emerged as dominant research domains, reflecting a broad interdisciplinary interest. Analysis of affiliations, authors, journals, and research areas unveiled multifaceted global involvement and thematic trends.

Further exploration could analyze publication types, temporal trends, domain-specific contributions, and institutional collaborations. Thematic analysis, collaborative networks, and in-depth examination beyond prolific authors or publishers offer avenues for deeper insights into AD research. In conclusion, this comprehensive analysis illuminates AD biomarker research's depth, breadth, and collaborative nature, serving as a foundational guide for future interdisciplinary endeavors and innovative methodologies in clinical practice.

5. CONCLUSION

The comprehensive bibliometric analysis conducted in this study offers a detailed and evolving portrayal of AD research focused on biomarkers and early diagnosis. Examining trends across PubMed and Web of Science databases revealed not just a quantitative surge in publications but also a qualitative evolution in methodologies and interdisciplinary collaborations. From dominant research domains like Neurosciences and Neurology to nuanced subdomains, the study highlighted the multifaceted nature of investigations. The global involvement of institutions underscores the collaborative and multinational efforts in

advancing insights into AD. Furthermore, insights into publisher trends, author contributions, thematic analysis, and collaborative networks illuminate the intricate web of expertise, collaboration, and evolving research themes within this critical domain. Overall, this comprehensive analysis underscores the depth, breadth, and collaborative nature of scholarly engagement, serving as a foundation for future interdisciplinary endeavors and innovative methodologies in AD research.

6. REFERENCES

ALVES, Luísa *et al.* Alzheimer's disease: a clinical practice-oriented review. *Frontiers in neurology*, v. 3, p. 63, 2012.

BOMASANG-LAYNO, Emily; BRONSTHER, Rachel. Diagnosis and Treatment of Alzheimer's Disease:: An Update. *Delaware journal of public health*, v. 7, n. 4, p. 74–85, set. 2021.

DONTHU, Naveen *et al.* How to conduct a bibliometric analysis: An overview and guidelines. *Journal of Business Research*, v. 133, p. 285–296, 2021. Disponível em: <https://www.sciencedirect.com/science/article/pii/S0148296321003155>.

DUBOIS, Bruno *et al.* Biomarkers in Alzheimer's disease: role in early and differential diagnosis and recognition of atypical variants. *Alzheimer's Research & Therapy*, v. 15, n. 1, p. 175, 2023. Disponível em: <https://doi.org/10.1186/s13195-023-01314-6>.

DUBOIS, Bruno *et al.* Clinical diagnosis of Alzheimer's disease: recommendations of the International Working Group. *The Lancet. Neurology*, v. 20, n. 6, p. 484–496, jun. 2021.

EDELBERG, H K; WEI, J Y. The biology of Alzheimer's disease. *Mechanisms of ageing and development*, v. 91, n. 2, p. 95–114, out. 1996.

KUMAR, Anil *et al.* Alzheimer Disease. Treasure Island (FL): [s.n.], 2023. .

PARK, Jung Eun *et al.* Diagnostic Blood Biomarkers in Alzheimer's Disease. *Biomedicines*, v. 10, n. 1, jan. 2022.

SILVA, Marcos Vinícius Ferreira *et al.* Alzheimer's disease: risk factors and potentially protective measures. *Journal of Biomedical Science*, v. 26, n. 1, p. 33, 2019. Disponível em: <https://doi.org/10.1186/s12929-019-0524-y>.

APPENDIX A

Detailed Search Strategy

Database 1
Pubmed/MEDLINE (https://pubmed.ncbi.nlm.nih.gov/)
Search date on December 6th, 2023

("Alzheimer's Disease"[Mesh] OR "Alzheimer Dementia"[Mesh] OR "Alzheimer Type Dementia"[Mesh] OR "Late Onset Alzheimer Disease"[Mesh] OR "Senile Dementia"[Mesh]) AND ("Biological Marker"[Mesh] OR "Biomarker"[Mesh] OR "Clinical Marker"[Mesh] OR "Biochemical Marker"[Mesh] OR "Laboratory Marker"[Mesh])

Filters: Year (2013 – 2023); Age: Aged (65+ years), Aged (80 and over: 80+ years).

Total: 2,525

Database 2
Web of Science (https://www.webofknowledge.com/)
Search date on December 6th, 2023

(TI=("Alzheimer's Disease") OR TI=("Alzheimer Dementia") OR TI=("Alzheimer Type Dementia") OR TI=("Late Onset Alzheimer Disease") OR TI=("Senile Dementia") OR TI=("Alzheimer's") OR TI=("AD")) AND (TI=("Biological Marker") OR TI=("Biomarker") OR TI=("Clinical Marker") OR TI=("Biochemical Marker") OR TI=("Laboratory Marker") OR TI=("Biomarkers") OR TI=("Markers") OR TI=("Diagnostic Marker") OR TI=("Prognostic Marker"))
Filters: Publications Years:
2013,2014,2015,2016,2016,2017,2018,2019,2020,2021,2022,2023

Total: 3,425