Original Article

A bibliometric analysis of global research trends on biomarker studies in Alzheimer's disease

Havva Yasemin Cinpolat [ID]

Department of Clinical Biochemistry, Çanakkale Onsekiz Mart University, Faculty of Medicine, Çanakkale, Türkiye

ABSTRACT

Objectives: The aim of this study was to examine trends in biomarker studies in Alzheimer's disease (AD)using bibliometric analysis.

Materials and methods: A bibliometric analysis was performed on research articles published about biomarkers in AD in the Scopus database. The data was retrieved from January 1, 1970 to October 27, 2021, using the keywords "biomarker" or "biomarkers" and "Alzheimer" or "Alzheimer's disease" in the search bar.

Results: A total of 1,385 articles were included in the study. The first article was published in 1995. Most of the articles were written in English [n=1,346 (97.18%)] and were from the United States of America (USA) [n=535 (38.62%)]. The most productive researchers and institutions were from Sweden.

Conclusion: Since AD is a global health problem, developing countries, as well as developed countries, should be encouraged to participate in biomarker studies on AD.

Keywords: Alzheimer's disease, bibliometric analysis, biomarker.

Dementias are a group of brain diseases that cause a decrease in cognitive functions. Alzheimer's disease (AD) is the most common cause of dementia worldwide.[1] The most common reason for the first admission in AD is short-term memory loss.[2] The disease progresses with changes in behavior and character; it also affects other cognitive areas such as thinking, decision making, and speaking. It eventually causes the loss of mental function, making the individual unable to perform daily activities.[3] The definitive diagnosis of AD is histopathological confirmation in autopsy materials.[4] The diagnosis of AD in clinical practice is based on the patient's medical history, clinical symptoms, and the exclusion of other causes of dementia. Biomarkers and structural imaging of the brain are also used in diagnosis.[5]

A biomarker is defined as a "human or animal biological property whose *in vitro* measurement or identification is useful for the prevention, diagnosis, prognosis, treatment, and follow-up of human or animal diseases, as well as their understanding".[6] Amyloid beta-protein, total tau, and phosphorylated tau as cerebrospinal fluid (CSF) biomarkers, and brain imaging techniques such as magnetic resonance imaging (MRI) or positron emission tomography (PET), are used in the diagnosis of AD.[7]

The Alzheimer's Disease Guide covers three stages of AD: preclinical, mild cognitive impairment (MCI), and Alzheimer's dementia. The preclinical stage is a process that includes amyloid deposition in the brain and some changes in nerve cells, in which clinical symptoms are unclear. At this stage, biomarkers are used for research, not in clinical practice. High tau and decreased beta-amyloid in CSF, decreased glucose uptake in PET, and atrophy in some parts of the brain in MRI are used as biomarkers in the MCI stage with mild memory problems and Alzheimer's dementia stage with memory loss as well as other cognitive and motor symptoms.[8] Even if some interventions are implemented after the diagnosis of AD, it

cannot be prevented or treated. Since pathological changes begin before typical symptoms appear, researchers have focused on biomarkers that can be used in the diagnosis of AD, especially in the preclinical stage.[9]

The aim of this study was to analyze global developments in biomarker studies in AD globally.

MATERIALS AND METHODS

Bibliometric analysis was carried out using data obtained from the Elsevier Scopus database. The Scopus database was accessed through the online library of Çanakkale Onsekiz Mart University. The data was retrieved from January 1, 1970 to October 27, 2021, using the keywords "biomarker" or "biomarkers" and "Alzheimer" or "Alzheimer's disease" in the search bar. Since the Scopus database is updated daily, data obtained in a single day was included to avoid bias. The authors, journals, countries, affiliations, funding sponsors, and publication date of the articles were all examined. Citation analyses were also performed. No country-year distinction was made.

Statistical analysis

The graphics of the Scopus database were used for visualization and also to create graphics Microsoft Office Excel 2010 (Microsoft Company, Seattle, USA) program was used. All of the data in the study was presented in percentages, numbers, and bar charts.

RESULTS

We reached a total 2,099 documents as a result of our search. Reviews (n=381), conference papers (n=81), and editorials (n=57) were also frequently published documents, with 1,385 (65.99%) of them being articles. Only articles were analyzed in our study as their higher scientific value.

The first article was published in 1995,[10] and the number of publications has increased since 2000, as shown in Figure 1.

Most of the articles were written in English (n=1,346, 97.18%). Also French, Spanish, Chinese, German, Japanese, Russian, Czech, Dutch, and Hungarian were the top 10 preferred languages.

The majority of the articles were written by authors from institutions based in the United States of America (USA) (n=535, 38.62%), the United Kingdom, and Germany were among the top three countries. Sweden, China, France, Italy, Spain, Netherlands, and Canada were in the top 10 countries on Alzheimer's and biomarker research. 841 (60.72%) of the articles were published in open access (OA) journals. Most of the articles were in the fields of medicine [n=965 (66.4%)] and neuroscience [n=678 (48.95%)] as well as biochemistry, genetics, and molecular biology [n=337 (24.33%)].

The most frequent keywords were 'Alzheimer's Disease' (n=1,251), 'Human' (n=1,201), 'Article' (n=1,115) and 'Biological Marker' (n=1,029).

The National Institute on Aging (n=348), the National Institutes of Health (n=345), and The United States Department of Health and Human Services (n=198) were the major funding sponsors. A total of 858 (61.94%) publications were funded by any affiliations.

The highest number of articles on the topic of Alzheimer's and biomarkers were published in the journals Journal of Alzheimer's Disease (n=199), Alzheimer's and Dementia (n=55), Alzheimer's Research and Therapy (n=42), Alzheimer's and Dementia Diagnosis Assessment and Disease Monitoring (n=41), and Neurobiology of Aging (n=40). The number of documents per year by source and comparisons of the number of document counts for up to five sources was given in Figure 2.

Kaj Blennow (Sweden) (n=72) and Henrik Zetterberg (Sweden) (n=70) were the most productive researchers on Alzheimer's and biomarker research. Sweden and the United
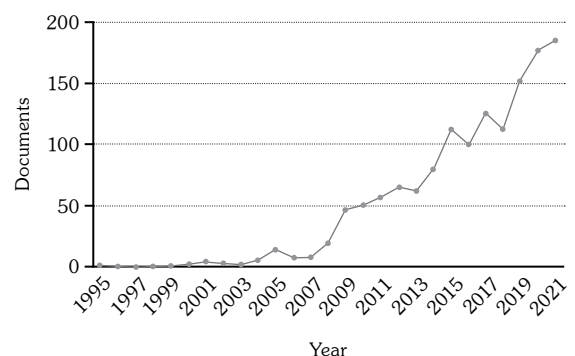
Figure 1. The number of publications over the years.
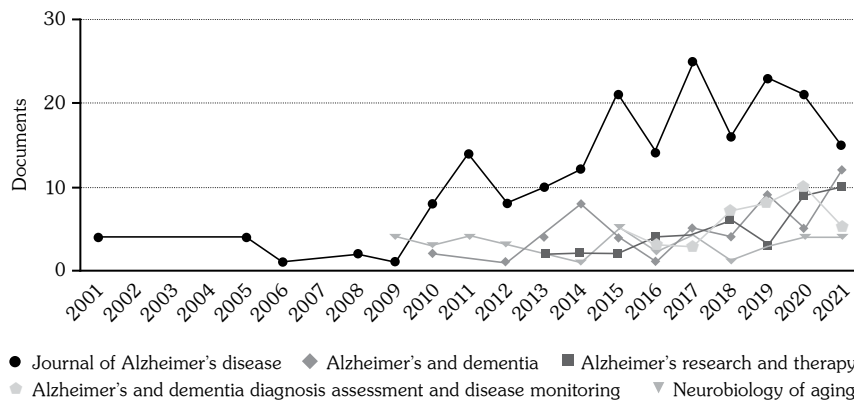
Figure 2. The most publishing journals on Alzheimer and biomarker studies.

Kingdom were the most productive countries in top-ranked affiliations on Alzheimer's and biomarker research, as shown in Table 1. There were no developing countries among the top 10 affiliations.[10-19]

Citing analysis

One hundred fifty-four (11.11%) of the articles had not yet been cited. Randall J. Bateman from Washington University School of Medicine in

Table 1. Top 10 affiliations on Alzheimer's disease and biomarkers research

Affiliation	Country	Number of articles
University of Gothenburg	Sweden	115
UCL Queen Square Institute of Neurology	United Kingdom	100
Sahlgrenska Academy	Sweden	95
University College London	United Kingdom	80
Sahlgrenska University Hospital	Sweden	80
Institut national de la santé et de la recherche médicale (Inserm)	France	66
Vu University Medical Center	Holland	60
University of California, San Francisco	USA	60
Massachusetts General Hospital	USA	59
Lund University	Sweden	52

UCL: University College London; USA: The United States of America.

Table 2. Citation analysis of the top 10 cited papers on Alzheimer's disease and biomarkers research

Authors	Year	Source	Number of citations	Open access
Bateman et al.,[11]	2012	New England Journal of Medicine	2,058	Yes
Shaw et al.,[12]	2009	Annals of Neurology	1,418	Yes
Hansson et al.,[13]	2006	Lancet Neurology	1,229	Yes
Mattsson et al.,[14]	2009	Journal of the American Medical Association (JAMA)	833	Yes
Haes et al.,[15]	2005	Journal of the American Chemical Society	751	No
Georganopoulou et al.,[16]	2005	Proceedings of the National Academy of Sciences of the United States of America	722	Yes
Cogswell et al.,[17]	2008	Journal of Alzheimer's Disease	659	No
Hensley et al.,[10]	1995	Journal of Neurochemistry	655	No
Tapiola et al.,[18]	2009	Archives of Neurology	602	Yes
Lannfelt et al.,[19]	2008	The Lancet Neurology	577	No

St. Louis (USA) was ranked first on the list of the most cited authors. Table 2 shows that the most cited articles were published in OA journals.

DISCUSSION

The evaluation of scientific productivity can be determined by using bibliometric studies. Top productive authors, affiliations, countries, etc. can all be evaluated using this method. The number of bibliometric analyzes has recently increased in the medical field. Bibliometric analyzes can be performed using pre-existing databases of publications on a subject, or they can be performed using datasets created by the researchers themselves, based on their preferences. The Web of Science, Scopus, and Medline are the most widely used bibliometric databases.[20-27] We preferred the Scopus database as it contains over 30,000 peer-reviewed journals from various disciplines (life sciences, social sciences, physical sciences, and health sciences).

In previous bibliometric studies,[22] images were created using additional programs (e.g., VOS viewer), but in our study, visualization was created solely using ready images and graphics from the Scopus database.

Although there are bibliometric studies on AD in the literature, no bibliometric analysis of publications on biomarkers in AD has been published to date.[28-31]

In all studies, the language of publication was generally English, and the most preferred language was also English (n=1,346, 97.18%) in our study.[25] This is because English is the most commonly used language in scientific literature.

While the first publications with Alzheimer's and biomarkers keywords in PubMed Medline were published in 1983[32,33] and in 1991 in Web of Science,[34] the first publication with the same keywords in our study according to Scopus was published in 1995.[10] The fact that different journals are included in the databases may explain why the results differ between the three databases. According to the search of all three databases, the number of publications with the keywords Alzheimer's and biomarkers has increased since the 2000s.

In all studies, the USA consistently ranks first in scientific productivity.[25] The USA similarly ranked first in the list of publications made by the country in our study. However, it was seen that the first institution was from Sweden and the second one was from England according to the top-ranked institutions in productivity. The top 10 countries in the ranking of biomarker studies in AD were developed countries while developing countries were not included in the top 10. Although 858 publications were not funded by any sponsor, the most funded sponsors were The National Institute on Aging [n=348], the National Institutes of Health [n=345], and The United States Department of Health and Human Services. This is thought to be because researchers in developed countries have easier access to resources. Alzheimer's disease is a major health issue all over the World, and it imposes an economic burden on countries. Therefore, biomarker studies for disease prevention and early diagnosis in developing countries should be supported, and researchers should focus their research on this area.

Nonetheless, the current study has limitations. Since the Scopus database was only used for research purposes, a bias may have occurred in this study. Studies in journals that are not indexed in the Scopus database, and also publications in local journals that are not listed in international indexes, could not be included. Consequently, we cannot claim that our study on Alzheimer's and biomarkers using a single database represents the entire literature.

In conclusion, although bibliometric analyses are the subject of social sciences, they have recently become more common in the field of medicine. As a result of our study, it has been observed that the number of publications in developing countries is low. Biomarker studies should be supported because AD is a global health problem that requires collaboration from all countries. We believe that biomarker studies in Alzheimer's disease should be guided, especially in developing countries, based on the bibliometric analysis we conducted in this study.

Ethics Committee Approval: Since this was not a human or animal study, the ethical committee approval was not required. The study was conducted in accordance with the principles of the Declaration of Helsinki.

REFERENCES

1. Prince MJ, Wimo A, Guerchet MM, Ali GC, Wu YT, Prina M. World Alzheimer Report 2015 - The Global Impact of Dementia. London: Alzheimer's Disease International; 2015.

2. Lashley T, Schott JM, Weston P, Murray CE, Wellington H, Keshavan A, et al. Molecular biomarkers of Alzheimer's disease: Progress and prospects. Dis Model Mech 2018;11:dmm031781.

3. Winblad B, Amouyel P, Andrieu S, Ballard C, Brayne C, Brodaty H, et al. Defeating Alzheimer's disease and other dementias: A priority for European science and society. Lancet Neurol 2016;15:455-532.

4. Hyman BT, Phelps CH, Beach TG, Bigio EH, Cairns NJ, Carrillo MC, et al. National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease. Alzheimers Dement 2012;8:1-13.

5. Dubois B, Feldman HH, Jacova C, Hampel H, Molinuevo JL, Blennow K, et al. Advancing research diagnostic criteria for Alzheimer's disease: The IWG-2 criteria. Lancet Neurol 2014;13:614-29.

6. Fuentes-Arderiu X. What is a biomarker? It's time for a renewed definition. Clin Chem Lab Med 2013;51:1689-90.

7. Blennow K, Zetterberg H. Biomarkers for Alzheimer's disease: Current status and prospects for the future. J Intern Med 2018;284:643-63.

8. Jack CR Jr, Albert MS, Knopman DS, McKhann GM, Sperling RA, Carrillo MC, et al. Introduction to the recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011;7:257-62.

9. Tan CC, Yu JT, Tan L. Biomarkers for preclinical Alzheimer's disease. J Alzheimers Dis 2014;42:1051-69.

10. Hensley K, Hall N, Subramaniam R, Cole P, Harris M, Aksenov M, et al. Brain regional correspondence between Alzheimer's disease histopathology and biomarkers of protein oxidation. J Neurochem 1995;65:2146-56.

11. Bateman RJ, Xiong C, Benzinger TL, Fagan AM, Goate A, Fox NC, et al. Dominantly Inherited Alzheimer Network. Clinical and biomarker changes in dominantly inherited Alzheimer's disease. N Engl J Med 2012;367:795-804.

12. Shaw LM, Vanderstichele H, Knapik-Czajka M, Clark CM, Aisen PS, Petersen RC, et al. Alzheimer's Disease Neuroimaging Initiative. Cerebrospinal fluid biomarker signature in Alzheimer's disease neuroimaging initiative subjects. Ann Neurol 2009;65:403-13.

13. Hansson O, Zetterberg H, Buchhave P, Londos E, Blennow K, Minthon L. Association between CSF biomarkers and incipient Alzheimer's disease in patients with mild cognitive impairment: a follow-up study. Lancet Neurol 2006;5:228-34.

14. Mattsson N, Zetterberg H, Hansson O, Andreasen N, Parnetti L, Jonsson M, et al. CSF biomarkers and incipient Alzheimer disease in patients with mild cognitive impairment. JAMA 2009;302:385-93.

15. Haes AJ, Chang L, Klein WL, Van Duyne RP. Detection of a biomarker for Alzheimer's disease from synthetic and clinical samples using a nanoscale optical biosensor. J Am Chem Soc 2005;127:2264-71.

16. Georganopoulou DG, Chang L, Nam JM, Thaxton CS, Mufson EJ, Klein WL, et al. Nanoparticle-based detection in cerebral spinal fluid of a soluble pathogenic biomarker for Alzheimer's disease. Proc Natl Acad Sci U S A 2005;102:2273-6.

17. Cogswell JP, Ward J, Taylor IA, Waters M, Shi Y, Cannon B, et al. Identification of miRNA changes in Alzheimer's disease brain and CSF yields putative biomarkers and insights into disease pathways. J Alzheimers Dis 2008;14:27-41.

18. Tapiola T, Alafuzoff I, Herukka SK, Parkkinen L, Hartikainen P, Soininen H, et al. Cerebrospinal fluid {beta}-amyloid 42 and tau proteins as biomarkers of Alzheimer-type pathologic changes in the brain. Arch Neurol 2009;66:382-9.

19. Lannfelt L, Blennow K, Zetterberg H, Batsman S, Ames D, Harrison J, et al. PBT2-201-EURO study group. Safety, efficacy, and biomarker findings of PBT2 in targeting Abeta as a modifying therapy for Alzheimer's disease: a phase IIa, double-blind, randomised, placebo-controlled trial. Lancet Neurol 2008;7:779-86.

20. Dindar Demiray EK, Durğun M, Alkan S. Examination of thesis on Aspergillosis: A Turkish sample. D J Med Sci 2021;7:103-6.

21. Yılmaz M, Alkan Çeviker S, Dindar Demiray EK, Uyar C. Türkiye'de cinsel yolla bulaşan hastalıklar ile ilgili yapılan lisansüstü tez çalışmalarının bibliyografik incelenmesi. Aksaray Üniversitesi Tıp Bilimleri Dergisi 2021;2:8-11.

22. Öntürk H, Dindar Demiray EK, Alkan S. Network analysis of nursing publications in the COVID 19 era. J Clin Med Kaz 2021;18:27-31.

23. Alkan Çeviker S, Yılmaz M, Uyar C, Dindar Demiray EK. Bibliometric analysis of scientific research on Crimean-Congo hemorrhagic fever in Turkey. D J Med Sci 2021;7:97-102.

24. Özlü C. Scopus veri tabanına dayalı bibliyometrik değerlendirme: Miyelodisplastik sendrom konulu yayınların global analizi ve Türkiye kaynaklı yayınların değerlendirilmesi. J Biotechinol & Strategic Health Res 2021;5:125-31.

25. Küçük U, Alkan S, Uyar C. Bibliometric analysis on infective endocarditis. Iberoamerican Journal of Medicine 2021;3:350-5.

26. Alkan S, Dindar Demiray EK, Yıldız E, Özlü C. Analysis of scientific publications on Acinetobacter bacteremia in Web of Science. Infect Dis Clin Microbiol 2021;3:39-44.

27. Didion CA, Henne WA. A Bibliometric analysis of folate receptor research. BMC Cancer 2020;20:1109.

28. Dong R, Wang H, Ye J, Wang M, Bi Y. Publication trends for Alzheimer's disease worldwide and in China: A 30-year bibliometric analysis. Front Hum Neurosci 2019;13:259.

29. Serrano-Pozo A, Aldridge GM, Zhang Q. Four decades of research in Alzheimer's disease (1975-2014): A bibliometric and scientometric analysis. J Alzheimers Dis 2017;59:763-83.

30. Li Y, Fang R, Liu Z, Jiang L, Zhang J, Li H, et al. The association between toxic pesticide environmental exposure and Alzheimer's disease: A scientometric and visualization analysis. Chemosphere 2021;263:128238.

31. Robert C, Wilson CS, Lipton RB, Arreto CD. Evolution of the research literature and the scientific community of Alzheimer's disease from 1983-2017: A 35-year survey. J Alzheimers Dis 2020;75:1105-34.

32. Terry RD, Katzman R. Senile dementia of the Alzheimer type. Ann Neurol 1983;14:497-506.

33. Delasnerie-Lauprêtre N, Calot M, Ohayon E, Foucault C, Cambon-de-Mouzon A, Clanet M, et al. Familial Alzheimer's disease: A study of HLA markers. Biomed Pharmacother 1983;37:186-8. French.

34. Matthews JC, Scallet AC. Nutrition, neurotoxicants and age-related neurodegeneration. Neurotoxicology 1991;12:547-57.