CEREBROSPINAL FLUID EVALUATION AS A DIAGNOSIS AND PROGNOSIS TOOL: A BIBLIOMETRIC ANALYSIS OF THE 100 MOST CITED ARTICLES

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ABSTRACT: Introduction: Cerebrospinal fluid (CSF) analysis is critical in the diagnosis, prognosis, and treatment of a wide range of diseases, including multiple sclerosis, encephalitis, meningitis, brain tumors, Creutzfeldt-Jakob disease, Alzheimer's disease, and other neurodegenerative conditions. Objective: Bibliometric analysis of the 100 most cited articles to obtain deeper insights into the status of research in this sector, in order to provide support for evidence-based medicine (EBM). Methodology: The main collection of the Web of Science was used to collect relevant studies on the topic, and the VOSviewer software was employed to build bibliometric networks. The examination did not include materials from editorials, books, patents, or research with unspecified designs. The articles chosen are in the time range from 1991 to 2020. Results: It was noted that most of the articles were human observational studies focusing on the diagnosis of neurodegenerative diseases, specifically Alzheimer's, which were published in neurology and/or Alzheimer's-related journals, mainly in the United States of America. We discovered forward-looking research hotspots and trends in this domain, which can serve as an important guide to neurological research, generating subsidies for medical decision-making. Conclusion: The number of primary articles on the subject points to the need for further future research on CSF associated, mainly, with other neurodegenerative diseases, in addition to Alzheimer's, sustaining the diagnostic efficacy and EBM.

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KEYWORDS: Cerebrospinal Fluid; Central Nervous System; Diagnosis; Prognosis; Neurodegenerative Diseases.

AVALIAÇÃO DO LÍQUIDO CEFALORRAQUIDIANO ENQUANTO FERRAMENTA DIAGNÓSTICA E PROGNÓSTICA: UMA ANÁLISE BIBLIOMÉTRICA DOS 100 ARTIGOS MAIS CITADOS

RESUMO: Introdução: A análise do líquido cefalorraquidiano (LCR) é fundamental no diagnóstico, prognóstico e tratamento de uma ampla gama de doenças, incluindo esclerose múltipla, encefalite, meningite, tumores cerebrais, doença de Creutzfeldt-Jakob, doença de Alzheimer e outras condições neurodegenerativas. Objetivo: Análise bibliométrica dos 100 artigos mais citados para obter insights mais aprofundados sobre o status da pesquisa nesse setor, a fim de fornecer subsídios para a medicina baseada em evidências (MBE). Metodologia: O acervo principal da Web of Science foi utilizado para coletar estudos relevantes sobre o tema, e o software VOSviewer foi empregado para construir redes bibliométricas. O exame não incluiu materiais de editoriais, livros, patentes ou pesquisas com desenhos não especificados. Os artigos escolhidos estão no intervalo de tempo de 1991 a 2020. Resultados: Observou-se que a maioria dos artigos eram estudos observacionais humanos com foco no diagnóstico de doenças neurodegenerativas, especificamente Alzheimer, que foram publicados em revistas de neurologia e/ou relacionadas ao Alzheimer, principalmente nos Estados Unidos da América. Descobrimos focos de pesquisa prospectivos e tendências nesse domínio, que podem servir como um importante guia para a pesquisa neurológica, gerando subsídios para a tomada de decisões médicas. Conclusão: O número de artigos primários sobre o tema aponta para a necessidade de novas pesquisas futuras sobre LCR associado, principalmente, a outras doenças neurodegenerativas, além da doença de Alzheimer, sustentando a eficácia diagnóstica e a BEM.
PALAVRAS-CHAVE: Líquido Cefalorraquidiano; Sistema Nervoso Central; Diagnóstico; Prognóstico; Doenças Neurodegenerativas.

EVALUACIÓN DEL LÍQUIDO CEFALORRAQUÍDEO COMO HERRAMIENTA DE DIAGNÓSTICO Y PRONÓSTICO: UN ANÁLISIS BIBLIOMÉTRICO DE LOS 100 ARTÍCULOS MÁS CITADOS

RESUMEN: Introducción: El análisis del líquido cefalorraquídeo (LCR) es crítico en el diagnóstico, pronóstico y tratamiento de una amplia gama de enfermedades, incluyendo esclerosis múltiple, encefalitis, meningitis, tumores cerebrales, enfermedad de Creutzfeldt-Jakob, enfermedad de Alzheimer y otras afecciones neurodegenerativas. Objetivo: Análisis bibliométrico de los 100 artículos más citados para profundizar en el estado de la investigación en este sector, con el fin de dar soporte a la medicina basada en la evidencia (MBE). Metodología: Se utilizó la colección principal de la Web of Science para recopilar estudios relevantes sobre el tema, y se empleó el software VOSviewer para construir redes bibliométricas. El examen no incluyó materiales de editoriales, libros, patentes o investigaciones con diseños no especificados. Los artículos elegidos están en el rango de tiempo de 1991 a 2020. Resultados: Se observó que la mayoría de los artículos eran estudios observacionales en humanos centrados en el diagnóstico de enfermedades neurodegenerativas, específicamente Alzheimer, que fueron publicados en revistas de neurología y/o relacionadas con el Alzheimer, principalmente en los Estados Unidos de América. Descubrimos puntos calientes de investigación con visión de futuro y tendencias en este dominio, que pueden servir como una guía

importante para la investigación neurológica, generando subsidios para la toma de decisiones médicas. Conclusión: El número de artículos primarios sobre el tema apunta a la necesidad de futuras investigaciones sobre el LCR asociadas, principalmente, con otras enfermedades neurodegenerativas, además del Alzheimer, manteniendo la eficacia diagnóstica y la MBE.
PALABRAS CLAVE: Líquido Cefalorraquídeo; Sistema Nervioso Central; Diagnóstico; Pronóstico; Enfermedades Neurodegenerativas.

1. INTRODUCTION

The cerebrospinal fluid (CSF) is a clear, colorless liquid that fills the ventricles of the brain and the subarachnoid space (CZARNIAK *et al.*, 2023; TUMANI; HUSS; BACHHUBER, 2017; WICHMANN; DAMKIER; PEDERSEN, 2022). It is mostly constituted of water, but it also contains protein, glucose, ions, vitamins, and neurotransmitters. It is created by the choroid plexus of the ventricular system, the interstitial space of the brain, and the subarachnoid space via passive ultrafiltration of fluid through capillaries and active ion transport by choroid plexus endothelial cells (MACAULAY; KEEP; ZEUTHEN, 2022). This production takes place mostly in the lateral ventricles, but it can also be observed in the third and fourth ventricles (CZARNIAK *et al.*, 2023; MACAULAY; KEEP; ZEUTHEN, 2022; TUMANI; HUSS; BACHHUBER, 2017; WICHMANN; DAMKIER; PEDERSEN, 2022).

CSF enters the brain and spinal cord's subarachnoid space via the Magendi's foramen and two lateral Luschka's foramina. Furthermore, CSF is absorbed mostly through the arachnoid granulations into the dural venous sinuses, from where it drains into the circulation (CZARNIAK *et al.*, 2023; MACAULAY; KEEP; ZEUTHEN, 2022; TUMANI; HUSS; BACHHUBER, 2017). Convective and pulsatile flow causes this movement in the central nervous system (CNS) (WICHMANN; DAMKIER; PEDERSEN, 2022).

In addition, this fluid serves a variety of essential tasks. It protects the brain from shocks and injuries caused by contact with the skull, reduces brain weight, transmits vital substances for CNS function, and eliminates waste products and hazardous substances from it. It also aids in the maintenance of CNS homeostasis by regulating electrolyte concentrations. It transports both neurotransmitters and hormones which enables the administration of specific drugs directly to the CNS (CZARNIAK *et al.*, 2023; TUMANI; HUSS; BACHHUBER, 2017; WICHMANN; DAMKIER; PEDERSEN, 2022).

Moreover, the cerebrospinal fluid (CSF) assumes critical importance in diagnosing and effectively treating a range of central nervous system (CNS) disorders, including multiple sclerosis, encephalitis, meningitis, brain tumors, Creutzfeldt-Jakob disease, Alzheimer's disease, and other neurodegenerative conditions. CSF can be collected through various methods, such as lumbar puncture, suboccipital puncture, or direct extraction from the lateral ventricles using external ventricular drainage (CZARNIAK *et al.*, 2023; WICHMANN; DAMKIER; PEDERSEN, 2022). Subsequently, multiple biomarker analyses can be conducted (HEPNAR *et al.*, 2019; RAHIMI; WOEHRER, 2018), which aid in detecting specific diseases, evaluating treatment efficacy, and understanding the origin of pathogenesis (CZARNIAK *et al.*, 2023; HEPNAR *et al.*, 2019; RAHIMI; WOEHRER, 2018).

Furthermore, the number of citations serves as a bibliometric parameter indirectly reflecting the impact, quality, and reputation of an article, journal, or author (BALDIOTTI *et al.*, 2021). Employing bibliometric analysis allows for the identification of highly cited papers, facilitating the characterization of scientific output within the relevant field of interest (KAROBARI *et al.*, 2021). While there are published bibliometric assessments that tangentially address the use of cerebrospinal fluid as a diagnostic and prognostic tool (CAI *et al.*, 2022; GUO *et al.*, 2022; LEI *et al.*, 2023; MONJAS-CÁNOVAS *et al.*, 2021; RAMOS-RINCON *et al.*, 2022; SAMANCI; SAMANCI; SAHIN, 2019; WU *et al.*, 2023; ZHANG *et al.*, 2016), direct exploration of its specific application remains lacking.

New approaches using CSF proteins as biomarkers for neurological diseases have been on the spotlight in the past few years, becoming an important field of study and revealing the need of reviews that integrate the knowledge so far in the area. This research will contribute to demonstrate what are the hotspots in CSF studies and if there are any clinical benefits of submitting patients to lumbar puncture. Thus, the objective of this study is to employ bibliometric parameters for identifying and characterizing the scientific literature concerning the use of CSF as a diagnostic and prognostic tool. By examining the 100 most cited articles on this subject, a comprehensive understanding of the current research landscape can be achieved.

2. METHODS

The Web of Science (WoS) core collection (WoS-CC) database was utilized to gather studies on the diagnosis of diseases through laboratory analysis of CSF on July 12, 2023, using the following search strategy: TS=("cerebrospinal fluid" OR "cerebrospinal liquor" OR "spinal fluid" OR "spinal liquor" OR "CSF" OR "brain fluid" OR "brain liquor") AND TS=("diagnosis" OR "disease diagnosis" OR "disease detection" OR "disease identification") AND TS=("cerebrospinal fluid analysis" OR "cerebrospinal fluid examination" OR "cerebrospinal fluid testing" OR "cerebrospinal fluid biomarkers" OR "cerebrospinal fluid markers" OR "cerebrospinal fluid proteins" OR "cerebrospinal fluid proteomics" OR "cerebrospinal fluid metabolomics" OR "cerebrospinal fluid neurochemicals" OR "cerebrospinal fluid neuroimaging").

Among the search of results related to CSF, the 100 most cited articles were based on citation numbers, abstracts, and complete texts by two independent researchers. Any disagreement was forwarded to a third researcher that was able to reach a primary consensus. Only articles related to the diagnosis by CSF analysis were included. Materials from editorials, books, patents, and articles with unspecified study designs were excluded.

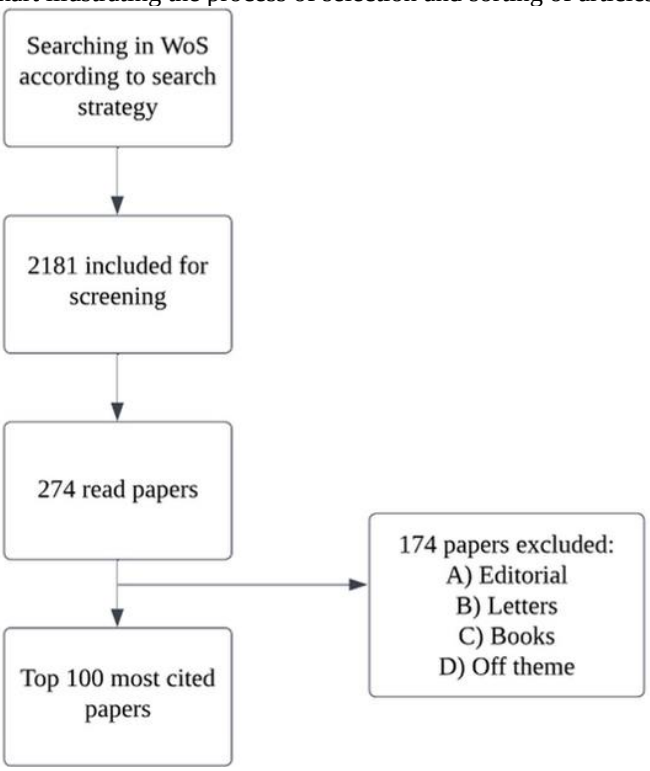
VOSviewer software (www.vosviewer.com) was employed to create co-authorship bibliometric networks and keyword roles. The software assigns nodes to clusters, where each cluster represents a set of closely related nodes. These clusters were represented by different colors. More important terms were depicted as larger nodes and strongly related terms were positioned close to each other. The lines connecting the nodes indicated cooperative relationships, with thicker lines representing stronger links between the specific two terms (SENGUPTA *et al.*, 2020; VAN ECK; WALTMAN, 2010).

3. RESULTS

3.1 General Data

Using the designated search strategy, a total of 2181 publications from the Web of Science main collection were identified in connection with cerebrospinal fluid (CSF) as a clinical marker for disease prognosis, as depicted in Fig. 1. These publications were then fully organized in descending order based on their citation frequency.

Figure. 1 Flowchart illustrating the process of selection and sorting of articles found in WoS.



Source: Elaborated by the authors (2023).

The 100 most cited articles are listed in Table 1 in descending order according to the total number of citations. The 100 most cited articles were described within a period referring to the years 1991 to 2020. The article "Neurosyphilis and human-immunodeficiency-virus type-1". JAMA Neurology. 1990, July (BERGER, 1991): is the oldest article, with 65 citations. Likewise, the article "Integrated proteomics reveals brain-based cerebrospinal fluid biomarkers in asymptomatic and symptomatic Alzheimer's disease". Sciences Advanced. 2020, October (HIGGINBOTHAM *et al.*, 2020): was the most recent article with the highest number of citations (n=77).

Table 1 The 100 most cited articles on the use of CSF as a diagnostic and/or prognostic tool.

Ranking	Authors and year of publication	Number of citations in the Wos-CC	Study design	Model	Studied diseases	CSF parameters
1	Janelidze *et al.* (2016)	359	Observational study	Human	Alzheimer's disease	β-amyloid (1-42) and β-amyloid (1-40)
2	Hall *et al.* (2012)	339	Observational study	Human	Parkinson's disease, Parkinson's disease with dementia, dementia with Lewy bodies, Alzheimer's	α-synuclein, β-amyloid (1-42), total tau, hyperphosphorylated tau, and neurofilament light chain

					disease, progressive supranuclear palsy, multiple system atrophy, and corticobasal degeneration	
3	Shi *et al.* (2011)	310	Observational study	Human	Parkinson's disease	Total tau, phosphorylated tau, β-amyloid (1-42), Flt3 ligand, and fractalkine
4	Freilich, Krol and Deangelis (1995)	299	Observational study	Human	Leptomeningeal metastasis	Cytology
5	Mulder *et al.* (2010)	251	Observational study	Human	Alzheimer's disease	β-amyloid (1-42), total tau, and phosphorylated tau
6	Shaw *et al.* (2011)	216	Observational study	Human	Alzheimer's disease	β-amyloid (1-42), total tau, and phosphorylated tau
7	Schoonenboom *et al.* (2012)	214	Observational study	Human	Alzheimer's disease, behavioral type frontotemporal dementia, semantic dementia, progressive nonfluent aphasia, dementia with Lewy bodies, vascular dementia, corticobasal degeneration, progressive supranuclear palsy, Creutzfeldt-Jakob disease, psychiatric disorder, and subjective memory complaints	β-amyloid (1-42), total tau, and phosphorylated tau
8	Brinkmalm *et al.* (2014)	183	Observational study	Human	Alzheimer's disease	Synaptosomal-associated protein 25
9	Gadoth *et al.* (2017)	175	Observational study	Human	Neurological autoimmunity	Leucine-rich-glioma-inactivated-1-immunoglobulin G and contactin associated protein-like 2-immunoglobulin G

10	Majbour *et al.* (2016)	165	Laboratory and observational study	Animal and human	Parkinson's disease and related disorders	Oligomeric and phosphorylated α-synuclein, total tau, phosphorylated tau, and β-amyloid (1-42)
11	Magdalinou *et al.* (2015)	164	Observational study	Human	Parkinson's disease, progressive supranuclear palsy, multiple system atrophy, corticobasal syndrome, Alzheimer's disease, and frontotemporal dementia	Total tau, phosphorylated tau, β-amyloid (1-42), neurofilament light chain, α-synuclein, amyloid precursor protein soluble metabolites α and β, monocyte chemoattractant protein-1, and chitinase-3-like protein 1
12	Thorsell *et al.* (2010)	160	Observational study	Human	Alzheimer's disease and mild cognitive impairment	Neurogranin, total tau, phosphorylated tau, and β-amyloid (1-42)
13	Parnetti *et al.* (2013)	152	Bibliographic study	Cellular, animal, and human	Parkinson's disease	α-synuclein, β-amyloid (1-42), total tau, lysosomal enzymes, and protein deglycase DJ-1
14	Wallin *et al.* (2010)	147	Observational study	Human	Alzheimer's disease	β-amyloid (1-42), total tau, and phosphorylated tau
15	Oschmann *et al.* (1998)	143	Observational study	Human	Neuroborreliosis	CSF cells, total protein, albumin, lactate, oligoclonal bands, and immunoglobulin G, A, and M for *Borrelia burgdorfei*
16	Snider *et al.* (2009)	141	Observational study	Human	Alzheimer's disease	β-amyloid (1-42), total tau, and phosphorylated tau
17	Parnetti *et al.* (2011)	136	Observational study	Human	Parkinson's disease, dementia with Lewy bodies, Alzheimer's disease, and frontotemporal dementia	β-amyloid (1-42), total tau, phosphorylated tau, and α -synuclein
18	Schindler *et al.* (2018)	135	Observational study	Human	Alzheimer's disease	β-amyloid (1-42), total tau, and phosphorylated tau
19	Tolboom *et al.* (2009)	134	Observational study	Human	Alzheimer's disease and mild cognitive impairment	Total cells, total protein, glucose, total tau, and β-amyloid (1-42)

20	Craig-Schapiro *et al.* (2011)	132	Observational study	Human	Alzheimer's disease	β-amyloid (1-42), total tau, and phosphorylated tau, Human Discovery Multi-Analyte Profile (MAP) 1.0 panel, and a Luminex 100 platform
21	Tedder *et al.* (1994)	131	Observational study	Human	Herpes-simplex virus infection and benign recurrent lymphocytic meningitis	PCR analysis for Herpes-simplex virus and anti-Herpes simplex virus antibodies
22	Mclean, Miller, and Thompson (1995)	130	Observational study	Human	Sarcoidosis, systemic lupus erythematosus, Behçet's disease with neurological involvement	CSF cells, immunoglobulin G content, isoelectric focusing of immunoglobulin G, and free light chain analysis
23	Parnetti *et al.* (2008)	129	Observational study	Human	Parkinson's disease with dementia, dementia with Lewy bodies, and Alzheimer's disease	β-amyloid (1-42), total tau, and hyperphosphorylated tau
24	Negrini, Kelleher, and Wald (2000)	129	Observational study	Human	Aseptic meningitis and bacterial meningitis	CSF cells, glucose, and protein
25	Stomrud *et al.* (2007)	128	Observational study	Human	Decline in subjective cognitive function and Alzheimer's disease	β-amyloid (1-42), total tau, and phosphorylated tau
26	Tarawneh *et al.* (2016)	126	Observational study	Human	Alzheimer's disease	Neurogranin, total tau, phosphorylated tau, and β-amyloid (1-42)
27	Orlovska-Waast *et al.* (2019)	121	Bibliographic study	Cellular, animal, and human	Schizophrenia and affective disorders	CSF cells, total protein, albumin, albumin ratio, immunoglobulins, interleukins, and specific CSF antibodies
28	Skillback *et al.* (2015)	120	Observational study	Human	Alzheimer's disease, vascular dementia, frontotemporal dementia, Parkinson's	β-amyloid (1-42), total tau, and phosphorylated tau

					disease dementia and dementia with Lewy bodies	
29	Kester *et al.* (2014)	117	Observational study	Human	Cerebral small-vessel disease and Alzheimer's disease	β-amyloid (1-42), total tau, and phosphorylated tau
30	Alves *et al.* (2014)	115	Observational study	Human	Parkinson's disease	β-amyloid (1-42), β-amyloid (1-40), β-amyloid (1-38), total tau, and phosphorylated tau
31	Alcolea *et al.* (2015)	113	Observational study	Human	Preclinical stages of Alzheimer's disease and suspected non-Alzheimer pathology	β-amyloid (1-42), sAPP beta, β-secretase activity, total tau, phosphorylated tau, and chitinase-3-like protein 1
32	Howard *et al.* (2002)	113	Observational study	Human	Traumatic and bloody lumbar puncture in acute lymphoblastic leukemia	CSF red blood cells
33	Al-Diwani *et al.* (2019)	106	Bibliographic study	Human	N-methyl-D-aspartate receptor-antibody encephalitis	CSF testing
34	Howell *et al.* (2017)	104	Observational study	Human	Alzheimer's disease	β-amyloid (1-42), β-amyloid (1-40), total tau, phosphorylated tau, soluble vascular cell adhesion molecule 1, soluble intercellular adhesion molecule 1, α -synuclein, and neurofilament light chain
35	de *Souza et al.* (2011a)	104	Observational study	Human	Alzheimer's disease, semantic dementia, behavioural variant frontotemporal dementia, posterior cortical atrophy, primary progressive non-fluent or logopenic	β-amyloid (1-42), total tau, and phosphorylated tau

					afasia, and functional cognitive disorders	
36	Nho *et al.* (2019)	100	Observational study	Human	Alzheimer's disease	β-amyloid (1-42), total tau, and phosphorylated tau
37	Lotankar, Prabhavalkar, and Bhatt (2017)	100	Bibliographic study	Cellular, animal, and human	Parkinson's disease	Glial fibrillary acidic protein, protein deglycase DJ-1, brain-derived neurotrophic factor, neurofilament light chain protein, α-synuclein, beta-glucocerebrosidase, neurosin, and homocysteine
38	Ruetschi *et al.* (2005)	100	Laboratory and observational study	Human	Frontotemporal dementia	Neurosecretory protein VGF, transthyretin, S-cysteinylated transthyretin, truncated cystatin C and chromogranin B
39	Petzold (2013)	98	Bibliographic study	Cellular and human	Multiple sclerosis	Intrathecal oligoclonal bands
40	Ohrfelt *et al.* (2016)	97	Observational study	Human	Alzheimer's disease	Synaptotagmin-1
41	Skiest (2002)	97	Bibliographic study	Human	Focal neurological disease in patients with acquired immunodeficiency syndrome	PCR of CSF specimens
42	de Souza *et al.* (2011b)	96	Observational study	Human	Posterior cortical atrophy and Alzheimer's disease	β-amyloid (1-42), total tau, and phosphorylated tau
43	Gandini *et al.* (2003)	95	Observational study	Animal	Fibrocartilaginous embolism	CSF cells, cytomorphological evaluation, and Pandy reaction
44	Sutphen *et al.* (2018)	94	Observational study	Human	Alzheimer's disease	Visinin-like protein 1, neurogranin, synaptosomal-associated protein 25, chitinase-3-like protein 1, β-amyloid (1-42), total tau, and phosphorylated tau

45	Brand *et al.* (2005)	93	Observational study	Human	Apparent life-threatening event	CSF culture, cell count, and chemistry
46	Wang *et al.* (2011)	92	Observational study	Human	Alzheimer's disease	β-amyloid (1-42), total tau, and phosphorylated tau
47	Zwan *et al.* (2014)	91	Observational study	Human	Alzheimer's disease and mild cognitive impairment	β-amyloid (1-42), total tau, and phosphorylated tau
48	Stoeck *et al.* (2012)	91	Observational study	Human	Rapid dementias (sporadic Creutzfeldt–Jakob disease, genetic Creutzfeldt–Jakob disease, iatrogenic Creutzfeldt–Jakob disease, variant Creutzfeldt–Jakob disease, Gerstmann–Stra¨ussler–Scheinker disease, fatal familial insomnia, neurodegenerative, inflammation, paraneoplastic /CNS tumour, stroke, epileptic fit, psychiatric, metabolic)	Protein 14-3-3, β-amyloid (1-42), total tau, and phosphorylated tau
49	Prashanth *et al.* (2016)	88	Observational study	Human	Parkinson's disease	β-amyloid (1-42), total tau, phosphorylated tau, and α-synuclein
50	Simon *et al.* (2015)	88	Observational and bibliographic study	Human	Bing-Neel syndrome	CSF cells, cytology, and protein
51	Pirzada, Ali, and Dafer (2000)	87	Observational study	Human	Fluorouracil-induced neurotoxicity	CSF cells, protein, glucose, stains, and culture
52	Counts *et al.* (2017)	85	Bibliographic study	Human	Alzheimer's disease	β-amyloid (1-42), total tau, phosphorylated tau, apolipoprotein isoforms, brain-derived neurotrophic factor,

						prostaglandin D2 synthase:transthyretin dimers, synuclein isoforms, ubiquitin, synaptosomal-associated protein 25, neurogranin, visinin-like protein 1, chitinase-3-like protein 1, neurofilament light chain, nerve growth factor, and chitinase-3-like protein 1
53	Nishimoto *et al.* (2004)	84	Observational study	Human	Fisher syndrome	CSF cells and protein
54	Matute-Blanch *et al.* (2018)	82	Observational study	Human	Multiple sclerosis	Chitinase 3 like 1, neurofilament light chain, and oligoclonal bands
55	Riedl *et al.* (2014)	80	Bibliographic study	Human	Frontotemporal lobar degeneration	β-amyloid (1-42), β-amyloid (1-40), and phosphorylated tau
56	Melah *et al.* (2016)	79	Observational study	Human	Alzheimer's disease	Chitinase-3-like protein 1, monocyte chemoattractant protein-1, neurofilament light chain protein, β-amyloid (1-42), total tau, and phosphorylated tau
57	Ferreira *et al.* (2014)	79	Bibliographic study	Human	Alzheimer's disease	β-amyloid (1-42), β-amyloid (1-40), and phosphorylated tau
58	Forgrave *et al.* (2019)	78	Bibliographic study	Human	Alzheimer's disease, frontotemporal dementia, and amyotrophic lateral sclerosis	Neurofilament light chain
59	Leen *et al.* (2013)	78	Bibliographic study	Human	Glucose transporter 1 deficiency	Glucose and lactate
60	Higginbotham *et al.* (2020)	77	Laboratory and observational study	Human	Alzheimer's disease	Total tau, β-amyloid (1-42), β-amyloid (1-40), neurofilament light, growth-associated protein 43, fatty acid-binding protein 3, chitinase-3 like-1, neurogranin,

						neurosecretory protein VGF, GPD dissociation inhibitor 1, SPARC-related modular calcium binding 1, and other proteins
61	Andersen *et al.* (2017)	77	Bibliographic study	Human	Parkinson's disease	Neurotransmitters, neuromodulators, oxidative stress markers, inflammatory markers, immunological markers, growth factors, and proteins involved in Parkinson's disease pathology
62	Struyfs *et al.* (2015)	76	Observational study	Human	Alzheimer's disease, frontotemporal dementia, dementia with Lewy bodies, and vascular dementia	β-amyloid (1-42), β-amyloid (1-40), β-amyloid (1-38), β-amyloid (1-37), total tau, and phosphorylated tau
63	Tosun *et al.* (2010)	76	Observational study	Human	Alzheimer's disease	β-amyloid (1-42), total tau, and phosphorylated tau
64	Nilselid *et al.* (2006)	75	Observational study	Human	Alzheimer's disease	Clusterin
65	Brinkmalm *et al.* (2018)	74	Laboratory and observational study	Human	Alzheimer's disease	β-amyloid (1-42), secretogranin-2, neurosecretory protein VGF, chromogranin A, neurexin-1, neuronal pentraxin-1, neurofascin, 2-microglobulin, cystatin C, amyloid precursor protein, lysozyme C, neurexin-2, neurexin-3, and neurocan core protein
66	Lautner *et al.* (2014)	74	Observational study	Human	Alzheimer's disease, mild cognitive impairment, bipolar disorder, and other dementias	β-amyloid (1-42), total tau, and phosphorylated tau

67	Hampel *et al.* (2018)	73	Observational study	Human	Alzheimer's disease, mild cognitive impairment, and frontotemporal dementia	β-amyloid (1-42), total tau, phosphorylated tau, neurofilament light chain, neurogranin, and chitinase-3-like protein 1
68	Chiasserini *et al.* (2017)	72	Observational study	Human	Alzheimer's disease, Parkinson's disease, and dementia with Lewy bodies	Fatty acid binding protein 3, α-synuclein, β-amyloid (1-42), total tau, and phosphorylated tau
69	Jabbari *et al.* (2020)	69	Observational study	Human	Progressive supranuclear palsy, corticobasal syndrome, and multiple system atrophy	β-amyloid (1-42) and total tau
70	Irwin, Trojanowski, and Grossman (2013)	68	Bibliographic study	Human	Frontotemporal lobar degeneration and Alzheimer's disease	β-amyloid (1-42), total tau, and phosphorylated tau
71	Huang *et al.* (2020)	66	Laboratory and observational study	Human	Multiple sclerosis	Subunit β of interleukin 12, interleukin-18 receptor 1, cluster of differentiation 5, macrophage inflammatory protein-1α, C-X-C motif chemokine ligand 9, C-X-C motif chemokine ligand 10, C-X-C motif chemokine ligand 19, vascular endothelial growth factor A, tumor necrosis factor receptor superfamily member 9, urokinase, fibroblast growth factor 19, monocyte chemoattractant protein 1, Monocyte chemoattractant protein 2, 4E-binding protein 1, macrophage inflammatory protein-1α,

						immunoglobulin G index, neurofilament light chain, eotaxin-1, oligoclonal bands, and CSF cells
72	Simonsen *et al.* (2016)	66	Bibliographic study	Human	Parkinson's disease, dementia with Lewy bodies, and multiple system atrophy	α-synuclein
73	Hebel, Dubaniewicz-Wybieralska, and Dubaniewicz (2015)	66	Bibliographic study	Human	Neurosarcoidosis	CSF cells, glucose, protein, angiotensin-converting enzyme, and oligoclonal bands
74	Davis (2014)	65	Bibliographic study	Human	Ocular syphilis	CSF cells, protein, and fluorescent treponemal antibody test
75	Tan, Yu, and Tan (2014)	65	Bibliographic study	Human	Alzheimer's disease	β-amyloid (1-42), total tau, phosphorylated tau, metalloproteinase 9, and chitinase-3 like-1
76	Hu *et al.* (2010)	65	Bibliographic study	Human	Alzheimer's disease, frontotemporal lobar degeneration, dementia with Lewy bodies, and Parkinson's disease	β-amyloid (1-42), total tau, phosphorylated tau, platelet-derived growth factor, neuron-glia CAM-related cell adhesion molecule, TAR DNA-binding protein 43, agouti-related protein, α-synuclein, and thymus-expressed chemokine
77	Berger (1991)	65	Observational study	Human	Neurosyphilis and human-immunodeficiency-virus type-1	CSF cells, protein, IgG, IgG index, oligoclonal bands, venereal disease research laboratory test, and fluorescent treponemal antibody-absorption test
78	Donovan *et al.* (2020)	64	Observational study	Human	Tuberculous meningitis	CSF cells, protein, glucose, MGIT culture, Xpert MTB/RIF Ultra (Xpert Ultra), and Xpert MTB/RIF (Xpert)

79	Moya-Alvarado *et al.* (2016)	63	Bibliographic study	Cellular, animal, and human	Alzheimer's disease	β-amyloid (1-42), total tau, phosphorylated tau, apolipoprotein A-1, apolipoprotein E, prostaglandin H2 D isomerase, transthyretin, heart fatty acid binding protein, neuronal pentraxin-2, neurosecretory protein VGF, secretogranin, neuronal cell adhesion molecule, chromogranin A, Rab3A, synaptotagmin, synaptosomal-associated protein 25, and neurogranin
80	Sonneville *et al.* (2009)	63	Bibliographic study	Human	Acute disseminated encephalomyelitis	CSF cells, protein, cultures, and oligoclonal bands
81	Singh *et al.* (2016)	62	Observational study	Human	Tuberculous meningitis	CSF cells, protein, glucose, culture, mycobacterial nucleic acids by polymerase chain reaction, bacterial screen with culture, cryptococcal latex antigen detection, antinuclear antibody, antineutrophil cytoplasmic antibody screen, hepatitis B and C, and angiotensin-converting enzyme level
82	Johansson *et al.* (2011)	62	Observational study	Human	Alzheimer's disease, mild cognitive impairment, and other dementias	β-amyloid (1-42), β-amyloid (X-42), β-amyloid (X-40), β-amyloid (X-38), total tau, phosphorylated tau, sAβPPα, and sAβPPβ
83	Krasnianski *et al.* (2006)	62	Observational study	Human	MM2 cortical subtype of sporadic Creutzfeldt-Jakob disease	S100B protein, 14-3-3 protein test, neuron-specific enolase, β-amyloid (1-42), and total tau

84	Vos *et al.* (2014)	60	Observational study	Human	Alzheimer's disease, subjective cognitive impairment, mild cognitive impairment, and dementia	β-amyloid (1-42), total tau, and phosphorylated tau
85	Okonkwo *et al.* (2010)	60	Observational study	Human	Alzheimer's disease and mild cognitive impairment	β-amyloid (1-42), total tau, and phosphorylated tau
86	Mattila *et al.* (1994)	60	Laboratory and observational study	Human	Alzheimer's disease and vascular dementia	Haptoglobin alpha-1 chains, CSF proteins, albumin, alpha-1-antitrypsin, haptoglobin (β-chains), transferrin, immunoglobulin G heavy and light chains, and prealbumin
87	Abdelnour *et al.* (2016)	59	Observational study	Human	Lewy body dementia	β-amyloid (1-42), total tau, and phosphorylated tau
88	Scheltens *et al.* (2016)	59	Observational study	Human	Alzheimer's disease	β-amyloid (1-42), total tau, and phosphorylated tau
89	Jesse *et al.* (2011)	59	Observational study	Human	Alzheimer's disease, Parkinson's disease, vascular dementia, frontotemporal lobar degeneration, progressive supranuclear palsy, multisystem atrophy, motor neuron diseases, spinocerebellar ataxia, and Huntington's disease	β-amyloid (1-42), total tau, CSF cells, lactate, albumin, immunoglobulin G, immunoglobulin A, immunoglobulin M, and oligoclonal immunoglobulin G bands
90	Moriarty *et al.* (1993)	59	Observational study	Animal and human	Acute lymphoblastic leukemia, T-cell acute lymphoblastic leukemia, B-cell acute lymphoblastic leukemia, chronic lymphocytic	Immunophenotyping of cytologic specimens by flow-cytometry (cluster of differentiation 1, 5, 9, 10, 19, 20, kappa, and lambda)

					leukemia, Burkitt's lymphoma, lymphoblastic lymphoma, large cell lymphoma, B-cell lymphoma, nodular lymphoma, and small lymphocytic lymphoma	
91	Wolfsgruber *et al.* (2017)	57	Observational study	Human	Subjective cognitive decline and mild cognitive impairment	β-amyloid (1-42), total tau, and phosphorylated tau
92	Llorens *et al.* (2016)	57	Observational study	Human	Alzheimer's disease, sporadic Creutzfeldt-Jakob disease, Lewy body dementia, normal pressure hydrocephalus, multiple sclerosis, vascular dementia, mild cognitive impairment, frontotemporal dementia, Parkinson's disease, fatal familial insomnia, and Gerstmann-Straussler-Scheinker syndrome	β-amyloid (1-42), β-amyloid (1-40), total tau, phosphorylated tau, and 14-3-3 protein test
93	Eckerstrom *et al.* (2013)	57	Observational study	Human	Mild cognitive impairment	β-amyloid (1-42), total tau, and phosphorylated tau
94	Hort *et al.* (2010)	57	Observational study	Human	Alzheimer's disease	β-amyloid (1-42), total tau, phosphorylated tau, antibodies against tubulins, neurofilaments, biomerieux, protein 14-3-3, light neurofilament, glial fibrillary acid protein, S100, S100B, glial

						fibrillary acidic protein, β-amyloid ratios, FACS, oligoclonal bands, and ferritin
95	Lehmann *et al.* (2014)	56	Observational study	Human	Alzheimer's disease, frontotemporal lobar degeneration, semantic dementia, dementia with Lewy bodies, Parkinson's disease, progressive supranuclear palsy, amyotrophic lateral sclerosis, normal pressure hydrocephalus, and psychiatric disorder	β-amyloid (1-42), total tau, and phosphorylated tau
96	Perani *et al.* (2016)	55	Observational study	Human	Alzheimer's disease, frontotemporal lobar degeneration, and dementia with Lewy bodies	β-amyloid (1-42), total tau, and phosphorylated tau
97	Lista *et al.* (2014)	54	Bibliographic study	Animal and human	Alzheimer's disease	β-amyloid (1-42), β-amyloid (1-40), β-amyloid (1-39), β-amyloid (1-38), β-amyloid (1-37), β-amyloid (1-17), β-amyloid (1-16), β-amyloid (1-15), β-amyloid (1-14), total tau, and phosphorylated tau
98	Abdo *et al.* (2004)	53	Observational study	Human	Parkinson's disease and multiple system atrophy	5-hydroxyindolacetic acid, 3-methoxy-4-hydroxyphenylethyleneglycol, total tau, neuron-specific enolase, and myelin basic protein, lactate, pyruvate, total protein, albumin ratio, S-100B, glial fibrillary acidic

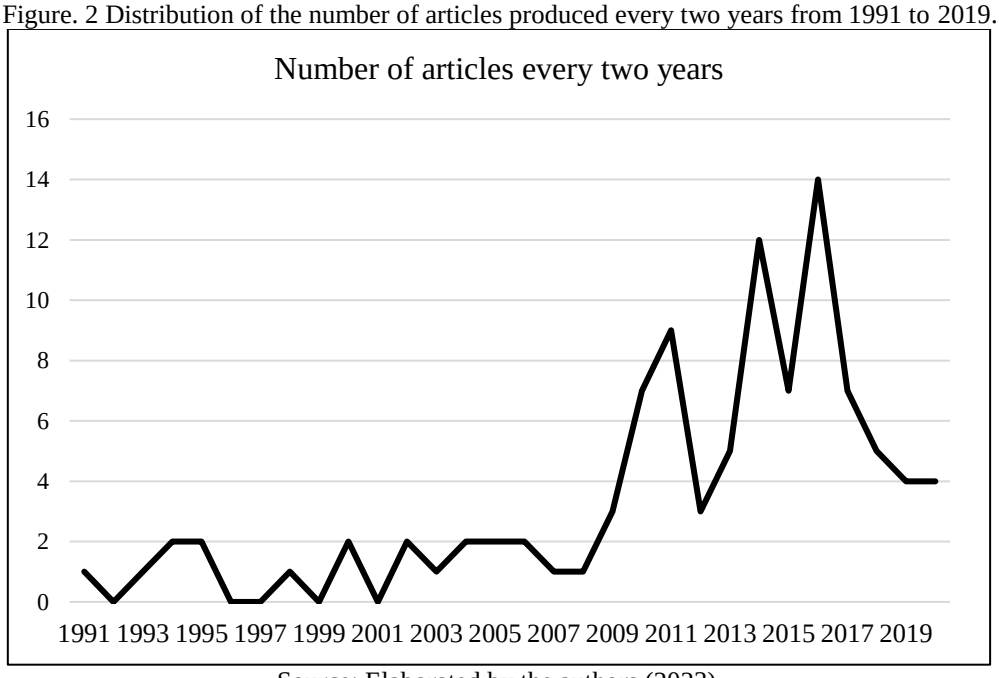
						protein, and homovanillic acid
99	Galluzzi *et al.* (2016)	51	Observational study	Human	Alzheimer's disease and mild cognitive impairment	β-amyloid (1-42), total tau, and phosphorylated tau
100	Lewczuk *et al.* (2015)	51	Bibliographic study	Animal and human	Alzheimer's disease and mild cognitive impairment	β-amyloid (1-42), β-amyloid (1-40), total tau, and phosphorylated tau

Source: Elaborated by the authors (2023).

3.2 Annual Scientific Production and Citations

All included studies were published between 1991 and 2020. An average annual growth, as of 2009, of 4.9% per year was noticeable. This growth has increased significantly in the last 10 years, with 2019 being the year with the greatest impact regarding the average citation per article, with an average value of 214.67 citations per article, followed by the year 1995, with a value of 214.5 citations per article. The most productive year was 2016 (n=14 articles), followed by 2014 (n=12 articles) and 2011 (n=9 articles). Annual publication output growth is shown in Fig. 2. In addition, the 10 most cited publications are shown in Table 2, along with the annual citation rate (ACR).

Figure. 2 Distribution of the number of articles produced every two years from 1991 to 2019.



Source: Elaborated by the authors (2023).

Table 2 Top 10 most cited articles classified according to their characteristics.

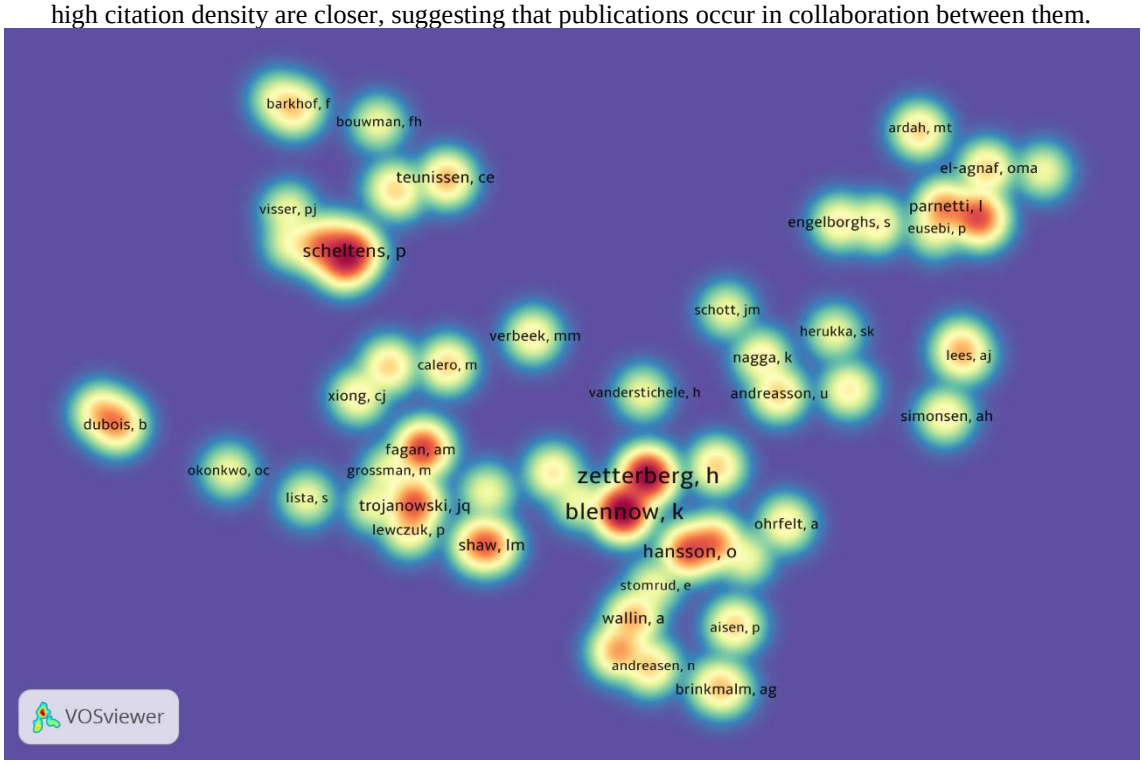
Authors	Year	Journal	Number of citations	ACR
Janelidze *et al.*	2016	Scientific Reports	359	44,88
Hall *et al.*	2012	Archives of Neurology	339	28,25
Shi *et al.*	2011	Annals of Neurology	310	23,85
Freilich, Krol, and Deangelis	1995	Annals of Neurology	299	10,31
Mulder *et al.*	2010	Clinical Chemistry	251	17,93
Shaw *et al.*	2011	Acta Neuropathologica	216	16,62
Schoonenboom *et al.*	2012	Neurología	214	17,83
Brinkmalm *et al.*	2014	Molecular Neurodegeneration	183	18,30
Gadoth *et al.*	2017	Annals of Neurology	175	25,00
Majbour *et al.*	2016	Molecular Neurodegeneration	165	20,63

Source: Elaborated by the authors (2023).

3.3 Distribution of Authors

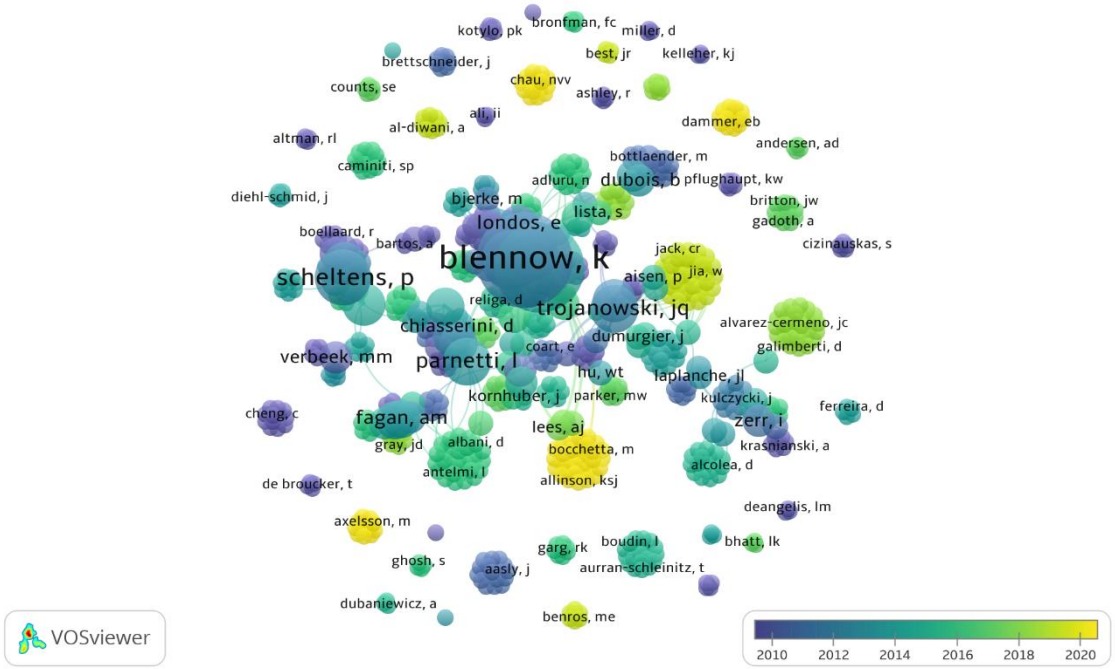
The authors of the 100 publications were analyzed and resulted in 5 main clusters. As for publications, the most prolific authors are Blennow, K (n=20 articles), followed by Zetterberg, H (n=18 articles), Hansson, O (n=9 articles), Scheltens, P (n= 8 articles), Minthon, L (n=7 articles), Parnetti, L (n=6 articles) and Trojanowski, JQ (n=6 articles). The other authors contributed values ≤ 5 articles. The number of citations of the authors can be seen in the heat map of Fig. 3. Co-authorship network is represented in Fig. 4.

Figure. 3 Representation of the clusters with the highest number of citations. Authors with the highest number of publications are represented by heat islands that demonstrate citation density. Authors with high citation density are closer, suggesting that publications occur in collaboration between them.



Source: Elaborated by the authors (2023).

Figure. 4 Co-authorship network demonstrating bibliographic coupling among the 818 authors of the 100 most cited articles. All authors form 59 clusters. The cluster size demonstrates the frequency of publications. The color scale represents the time interval of the publications. The authors with the highest publication number are superimposed on the authors with the lowest publication number.



Source: Elaborated by the authors (2023).

3.4 Distribution of Journals and Countries

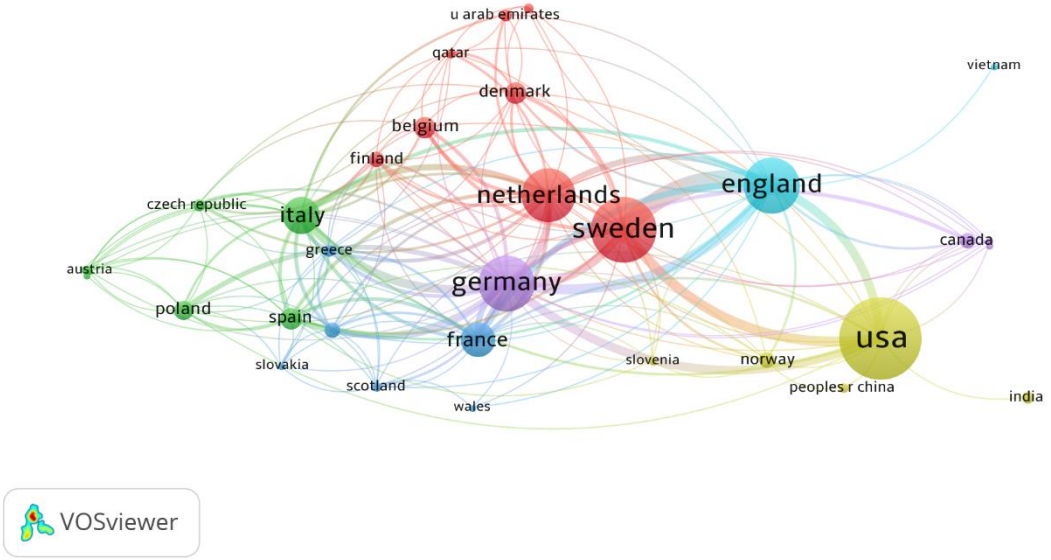
The distribution of all 100 publications covered 22 countries/regions. The top 10 countries are shown in Table 3. The United States of America ranked first with a total publication of 27 articles, followed by Sweden with 15 articles, Germany with 10 articles, and the Netherlands with 10 articles. Likewise, the ranking of the most cited countries was not so different, with the USA with 2974 citations, followed by Sweden with 2041 citations, the Netherlands with 1155 citations, and Germany with 720 citations. The collaboration network is represented in Fig. 5.

Table 3 Top 10 countries in descending order in scientific production.

Countries	Articles	Number of citations
United States of America	27	2974
Sweden	15	2041
Germany	10	1155
Netherlands	10	720
Italy	7	690
France	6	480
India	3	339
Spain	3	274
United Kingdom	3	250
Denmark	2	198

Source: Elaborated by the authors (2023).

Figure. 5 Co-occurrence network of countries with the highest number of articles on the subject. The cluster size demonstrates the higher frequency of publication of studies. The thickness of the line between the nodes represents the strength of the link between the countries being demonstrated by thicker lines.



Source: Elaborated by the authors (2023).

Regarding the distribution of journals, the Journal of Alzheimer's Disease had the greatest relevance in terms of the number of articles, with 7 articles, followed by the Journal of Alzheimer's & Dementia, with 6 articles, Archives of Neurology with 5 articles, and Brain with 4 articles. The top 10 journals with the number of articles published are shown in Table 4.

Table 4 Top 10 most relevant journals with their respective Impact Factor.

Journal	Impact Factor	Number of articles
Journal of Alzheimer's Disease	4.160	7
Alzheimer's & Dementia	14	6
Archives of Neurology	7.108	5
Brain	15.250	4
JAMA Neurology	11.580	4
Journal of Neurology, Neurosurgery, and Psychiatry	13.654	4
Neurology	8.800	4
Alzheimers Research & Therapy	8.823	3
Annals of Neurology	11.274	3
Journal of Neurology	6.682	3

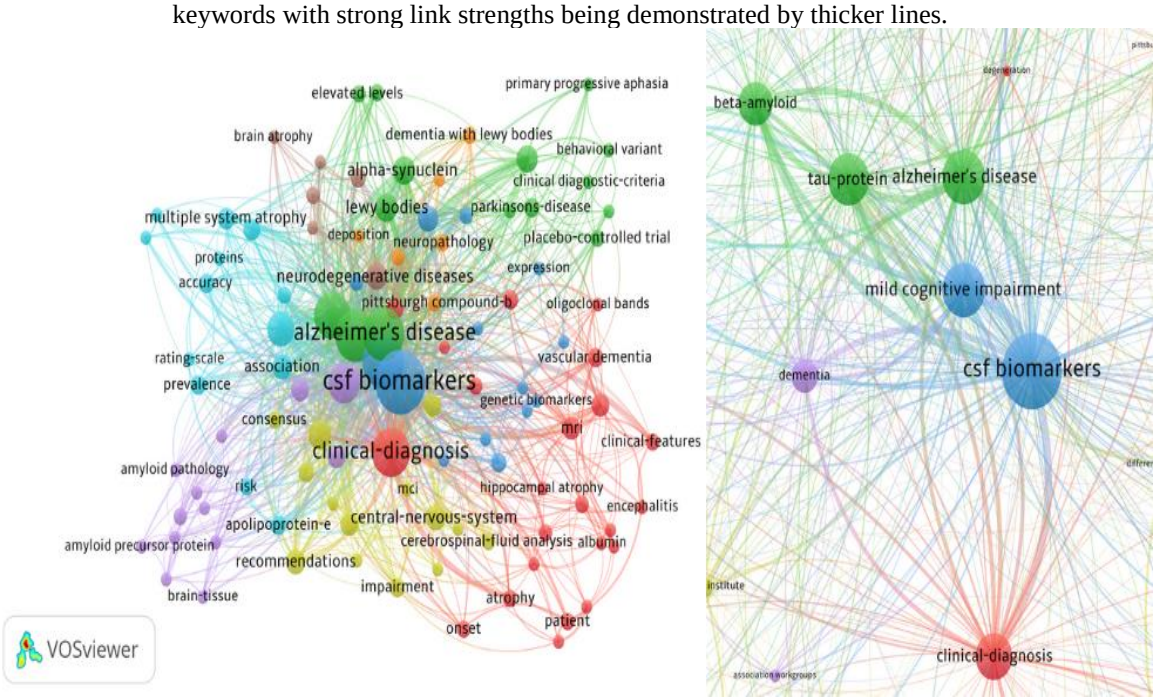
Source: Elaborated by the authors (2023).

3.5 Distribution of Keywords

All 602 keywords were generated using VOSviewer. We selected only the keywords that occurred in at least 2 articles, identifying a total of 104. The most frequent keywords were represented by occurrence networks as shown in Fig. 6. The most frequent

term used was CSF biomarkers (n=67), followed by Alzheimer's Disease (n=42), Mild Cognitive Impairment (n=42), Tau-protein (n=40), and Beta-amyloid (n=31).

Figure. 6. Co-occurrence network of keywords visualized in VOSviewer. The node size represents the frequency of the author keyword with larger nodes indicating greater frequency. The color of the node represents the possibility of co-occurrence of author keywords among the 100 most cited articles with nodes of the same color demonstrating that there is co-occurrence between author keywords in the same article. The thickness of the line between the nodes represents the strength of the link between the author's keywords with strong link strengths being demonstrated by thicker lines.



Source: Elaborated by the authors (2023).

4. DISCUSSION

In this study, a bibliometric analysis was conducted to quantify and visualize trends in publications and research focal points in the field of cerebrospinal fluid (CSF) analysis as a diagnostic tool for disease detection. The research revealed a substantial increase in studies related to CSF analysis, with the United States of America being the prominent driving force due to its high academic standing, reflected by a considerable number of publications and citations attributed to this country. However, it was observed that only one developing country, India, was among the top 10 prolific countries in Table 2 over the last 30 years. This highlights the need for increased collaboration between developed and developing nations to promote advancements in this field.

Another noteworthy aspect pertains to the analysis of cited references. Notably, terms like "CSF biomarkers," "Alzheimer's Disease," "Mild Cognitive Impairment," "Tau-protein," and "beta-amyloid" emerged as key hotspots in the research on CSF

diagnostics. These biomarkers in cerebrospinal fluid hold prognostic significance for disease monitoring, differential diagnosis, and survival analysis, primarily in neurodegenerative disorders such as Alzheimer's, Parkinson's, and multiple sclerosis (JOHNSON *et al.*, 2020; LO SASSO *et al.*, 2019; PARNETTI *et al.*, 2019). Additionally, other references discussed clinical prognosis and diagnosis of infectious pathologies like meningitis, neurosyphilis, and neurosarcoidosis, as well as dementia-related conditions like frontotemporal degeneration and dementia with Lewy bodies. This emphasizes the valuable contribution of laboratory analysis of biomarkers in CSF for diagnosing and proposing certain nervous system diseases (BAICHURINA *et al.*, 2021).

CSF analysis offers a major advantage in identifying specific biomarkers associated with various neurodegenerative pathologies, as evidenced in the articles. For instance, abnormal levels of tau protein and beta-amyloid are commonly found in the CSF of Alzheimer's patients, while α-synuclein serves as a key biomarker for diagnosing Parkinson's disease. The presence of β-amyloid in the CSF is also an important indicator of Alzheimer's (JEROMIN; BOWSER, 2017). Moreover, CSF analysis plays a crucial role in detecting CNS infections and inflammation. The presence of inflammatory cells such as lymphocytes, neutrophils, and macrophages, along with elevated levels of inflammatory proteins, signifies an active immune response, aiding in the differential diagnosis of diseases like meningitis and encephalitis and enabling prompt and appropriate treatment (JULIÁN-JIMÉNEZ; MORALES-CASADO, 2019). In suspected multiple sclerosis cases, the presence of oligoclonal bands of immunoglobulin G in the CSF confirms immune activation in the central nervous system, supporting the diagnosis (LO SASSO *et al.*, 2019).

Furthermore, Batista, Barbosa, and Dias (2022) conducted a literature review on the pathophysiology, etiology, and diagnosis of bacterial meningitis. The emphasis was primarily on diagnostic accuracy when using cerebrospinal fluid (CSF) and the continuous evolution of this tool. This enables the achievement of extremely high sensitivity, even in differentiating the etiological agent of the infection. In the case of bacterial meningitis, this will be of paramount importance since the correct choice of antimicrobial therapy will depend on this result (BATISTA; BARBOSA; DIAS, 2022).

The most frequently used keywords among the 100 articles underscored a significant focus on diseases like Alzheimer's, Parkinson's, and mild cognitive impairment. This highlights the necessity for further research in cerebrospinal fluid

biomarkers to aid in the diagnosis of these diseases and complements other modalities for monitoring clinical prognosis.

It is crucial to acknowledge an important limitation of CSF analysis, as it may not be definitive for diagnosing several diseases. Interpretation of results must be combined with clinical information, imaging data, and other laboratory tests to achieve accurate diagnosis. Furthermore, reference values for CSF analysis may vary among different laboratories, posing challenges in result comparison. Hence, it is essential to consider these variabilities and perform serial analyses when required.

5. CONCLUSIONS

This bibliometric study provides a comprehensive analysis of global research trends in cerebrospinal fluid (CSF) analysis over a 30-year period and demonstrates that this approach is an important tool for diagnosis and prognosis of neurological patients, mostly for those with neurodegenerative diseases. The identification of potential collaborators, institutions, hotspots, and future research trends contributes valuable insights for guiding future investigations in the clinical diagnostic and prognostic utility of CSF analysis. Moreover, the findings underscore the importance of conducting further research to gain a deeper understanding of significant CSF mechanisms relevant to other neurodegenerative diseases, thereby enhancing diagnostic efficacy.

Furthermore, this research achieves great results and provides background and theoretical support for scientists investigating new approaches to understand neurological diseases. Also, new diagnosis tools and prognosis markers are clinically important to the patients and their physicians. The study limitations were related to the possibility that recent relevant articles in the field do not present a significant number of citations, leaving them out of this research.

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