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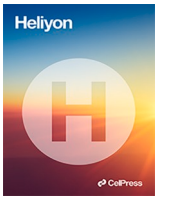

Research article

Global research trends on the links between NfL and neurological disorders: A bibliometric analysis and review

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ABSTRACT

Background: The global incidence of neurological diseases has been on the rise, creating an urgent need for a validated marker. Neurofilament Light Chain (NfL) holds promise as such a marker and has garnered significant attention in the field of neurological diseases over the past decades.
Methods: Corresponding articles from 2013 to 2023 were collected from the Web of Science database, and data were analyzed by CiteSpace and VOSviewer software.
Results: A total of 1350 articles were collected from 296 countries/regions, involving 7246 research organizations. Since 2013, among the top ten institutions and authors with the highest number of published papers, the most are from the US and the UK. The United States leads in the number of published papers, but England holds a more momentous position, because it has higher IF. Henrik Zetterberg is the most influential scholar in the field.
Conclusions: The output of papers mainly relies on researchers from developed countries, and scholars from the United States and England have contributed the largest number of papers. Until now, the importance of NfL in neurological diseases has attracted global attention. In addition, NfL contributes to the potential diagnosis of various neurological disorders and can be used to improve the accuracy of differential diagnosis and prognostic assessment as well as predict the response to treatments. More and more in-depth studies are highly needed in the future.

1. Introduction

Neurological disorders have a huge impact on society. For adults, they make it difficult to live a stable life in society, and young children and the elderly are at even higher risk for neurological disorders. Over the past three decades, neurological disorders have been the second leading cause of death worldwide, and anytime society faces an aging population in the future, the incidence of neurological disorders such as alzheimer disease (AD) needs to be taken seriously. Neurofilament proteins (Nfps) are a hot topic of research in the diagnosis and treatment of neurological diseases [1]. Nfps have undergone progressive development since its discovery,

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emerging as the most promising blood biomarker for neural axonal degeneration or injury at present, and quantifying axonal damage in neurological disorders enhances diagnostic precision and prognostic assessment [2]. Nfps are involved in forming the cytoskeleton of neurons. Mature mammalian neurons typically express five different NfPs: the NfL, neurofilament medium (NfM) chain and neurofilament heavy (NfH) chain, as well as internexin neuronal intermediate filament protein alpha (INA) and peripherin (PRPH) [2]. However, NfL is the only subunit in Nfps that can self-assemble into functional fibers. NfL is present in dendrites and neuronal soma, as well as in larger myelinated axons, where their expression is particularly high [3]. NfL plays a vital role in promoting the growth and conferring structural stability to neurons of neural axons in the central nervous system (CNS) and peripheral nervous system (PNS) [4,5]. Under physiological conditions, small amounts of NfL are released during brain development, maturation, and aging. However, when axonal injury or neuronal degeneration occurs, NfL responds to the injury and can form abnormal neuronal aggregates in neurodegenerative disorders. It is released in large quantities into the interstitial fluid, cerebrospinal fluid (CSF), and bloodstream (Fig. 1). Therefore, the researcher assessed the change of neurofilaments, especially NfL, in CSF and peripheral blood to quantify neuronal injury or neurodegeneration [6–8].

Although enzyme-linked immunosorbent assay (ELISA) was the first method to measure NfL, the analytical sensitivity of ELISA precludes its general use for measuring NfL in peripheral blood [9]. The introduction of electrochemiluminescent assays represented a major technological advance, enabling the measurement of neurofilaments in the blood of patients with neurological disorders [10], thus changing the NfL test from an invasive CSF test to a blood test. In 2015, the first ultra-sensitive assay for NfL was introduced by enhancing the ELISA signal using single-molecule array (Simoa) technology. This assay accurately measures low levels of NfL in peripheral blood, even in people without PNS or CNS pathology [11,12]. However, current Simoa detection technologies are difficult

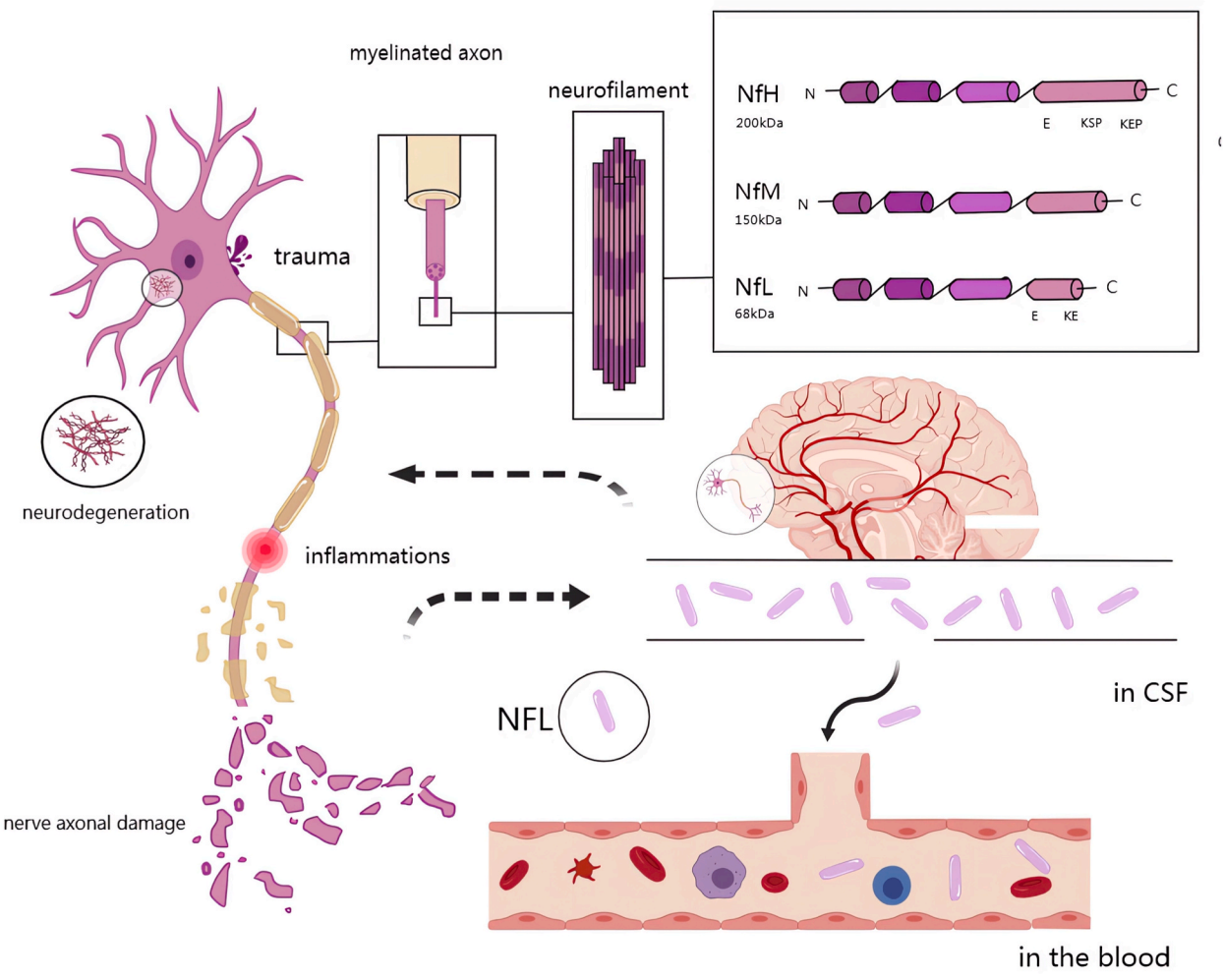

Fig. 1. Explanation. Nf typically express five different NfPs: the NfL, NfM, and NfH chains, INA, and PRPH. Nf proteins have a typical IF structure consisting of an amino-terminal "head" structural domain, a central alpha-helical "rod" structural domain, and a carboxyl-terminal "tail" structural domain, and the tails are usually enriched with glutamine repeat sequences. NfM and NfH contain multiple highly NfM and NfH contain multiple highly phosphorylated KSP repeat sequences. Under physiological conditions, the body releases small amounts of NfL, but during inflammation, trauma, neurodegeneration, or axonal injury, NfL forms abnormal neuronal aggregates and is released in large quantities into the CSF and blood.

to apply on a large scale due to their limited proliferation outside of major research centers and relatively high cost. Recently, methods have also been developed for the detection of plasma NfL using Meso Scale Discovery, immunomagnetic reduction techniques and the microfluidic channel-based Ella platform [13–15].

Numerous prior studies have corroborated the notion that NfL can serve as a reliable biomarker. Extensive research has explored the role of NfL in neurological disorders such as multiple sclerosis (MS), frontotemporal dementia (FTD), amyotrophic lateral sclerosis (ALS), AD, atypical parkinson's disease (APD), and traumatic brain injury. Nevertheless, there remains a relative paucity of research investigating the role of NfL in the neurological complications of Creutzfeldt-Jakob disease and human immunodeficiency virus (HIV) infection, huntington's disease (HD), and normal pressure hydrocephalus.

Bibliometric analysis is a scientific approach that focuses on the study of literature or literature-related media. It employs mathematical, statistical, and other measurement methods to investigate the patterns and scientific management of literature and literary systems. Moreover, it delves into the dynamic characteristics of science and technology. Applying bibliometrics to a specific field enables researchers to conduct further investigations in that area. In this context, biometric visualization and analysis are performed using tools like VOSviewer and CiteSpace to visualize the research development history, current research status, research hotspots, and development trends related to the role of NfL in neurological diseases research.

2. Materials and methods

The search strategy in this article includes synonyms for NfL and neurological disorders. In the present study, the inclusive and exclusion criteria were as follows: (i) the timespan ranged from 2013 to 2023, encompassing 10 years in total; (ii) only articles and reviews were included; (iii) setting species limits, selecting only humans; (iv) publication language is English. The search results were screened using WoS, and literature that met the search requirements was exported to CiteSpace 6.2.3 and VOSviewer 1.6.19 for further analysis. Fig. 2 illustrates the data handling process. A total of 1128 articles and 222 reviews were screened and analyzed.

3. Results

3.1. Analysis of country

A total of 296 countries/regions participated in the analysis. Table 1 presents the top ten countries with the highest number of

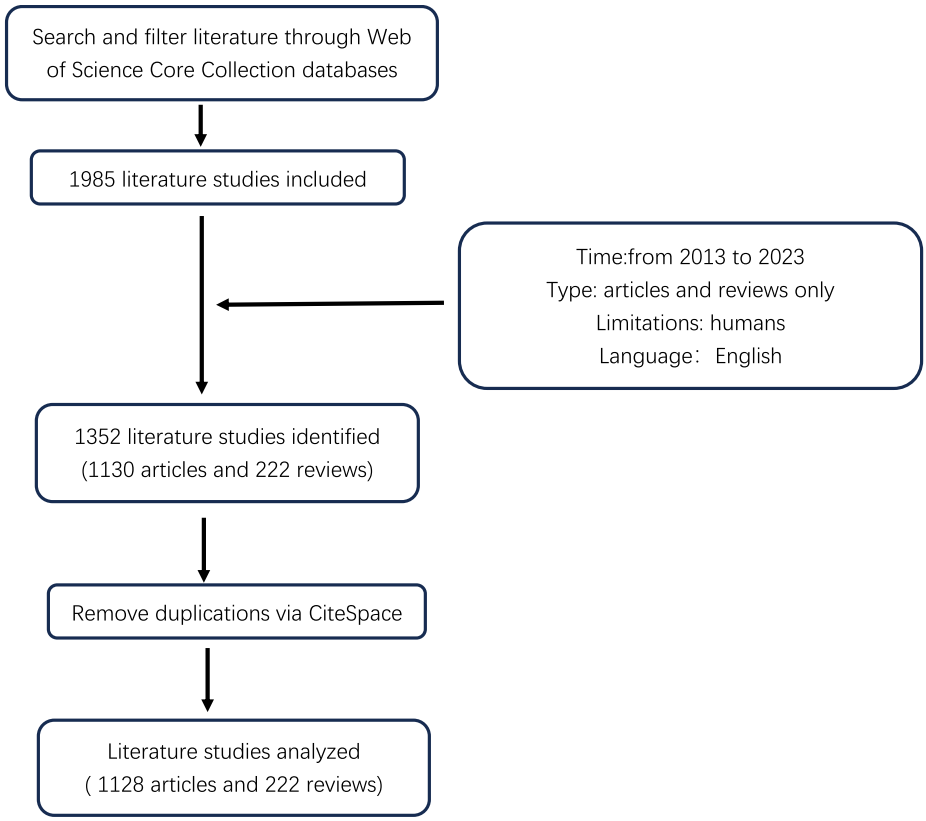

Fig. 2. Flowchart of data processing.

articles produced. The USA stands out as the leading contributor with 393 documents (29.1 %), followed by England (22.3 %), Sweden (19.1 %), Germany (18.9 %), Italy (13.9 %), and Switzerland (12.1 %). Among the top ten countries, only USA and England hold more than 300 articles. Therefore, it can be inferred that England and USA are the most active countries in terms of relevant research in this field. However, despite the USA having the highest number of publications, the number of citations in England is significantly higher. Fig. 3 shows the relationship between the top countries according to the number of publications. Notably, nodes represented in purple indicate a higher node mediated centrality value above 0.1, reflecting the key centrality. England and the USA have mediating centralities of 0.24 and 0.23, respectively, indicating their crucial bridging role in research within this field. In summary, the United States has been the most prolific and influential country in this research area. Additionally, Germany, despite starting its research relatively late, has made significant contributions in the past decade, aligning with trends in neuroscience.

3.2. Institutions

Fig. 4 illustrates that the number of articles issued is increasing from year to year and at a significant rate. This trend can be categorized into three phases: the " budding period ", the " stable growth period " and the " rapid development period ". During the " budding period " (2012–2013), the role of NfL in neurological disorders was in its early stages and had not garnered much attention from scientists. Only 15 articles were published during these two years. In the “stable growth period” (2014–2016), the research in this field saw an increase compared to the budding period, although the annual output still exhibited relatively slow growth. The turning point came in the " period of rapid growth " (2017–present), as evident from 2017 onwards. The annual output of articles experienced a substantial surge, indicating that research in this field gained widespread attention and became a prominent hotspot of scientific interest.

Table 2 lists the top 10 institutions according to the number of publications, with the top five being: University of Gothenburg, Sahlgrenska University Hospital, London’s Global University, UCL Queen Square Institute of Neurology and University of Basel. Fig. 5 shows the institutional association mapping processed using Citespace. The size of the circles is proportional to the number of articles issued, and different colors of the circles correspond to different years. In addition, to clearly describe the collaborative relationships between institutions, we analyzed the institutional co-occurrence map using Citespace (Fig. 5a). This map highlights co-occurrence relationships between institutions with more than 20 papers (Fig. 5b).

3.3. Author analysis

According to the number of published articles, Henrik Zetterberg was the most prolific author with 184 articles, accounting for 13.62 % of the retrieved articles, making him the author who conforms to Lotka’s Law. Analyzing authors of highly cited papers in the field, it is noteworthy that Henrik Zetterberg (Zetterberg, Henrik) ranks first in terms of citations, with 9752 citations, and he also holds the record for the highest number of publications, indicating his prominent presence and prestige in the research field. Following closely were Jens Kuhle (9.70 %), Kaj Blennow (9.33 %) (Fig. 6). The top three authors collectively contributed to one-third of the total number of publications. The main body of literature in the field appears to be dependent on a select few authors. Authors who have published more than eight papers (inclusive of eight papers) are considered core authors in the field, according to the Price theorem. There are 35 authors.

3.4. Journal same citation analysis

As shown in Table 3, the journal with the highest number of publications is " Journal of Neurology ". However, the most cited journal on average is " Neurology ". The most cited article in the journal is titled " Neurofilaments as Biomarkers in Neurological Disorders ", this article holds pivotal importance for the field [16].

Fig. 7 illustrates the top fourteen journal associations based on citations. The journal associations show roughly two clusters. Since " Neurology " is co-cited the most, it corresponds to the largest node and is strongly associated with other journals. It is worth noting that " Neurology " is also the journal with the highest average number of citations, which indicates that there are articles published by it that have made outstanding contributions to the field.

Table 1
Ranking of top 10 countries in terms of publications.

Country	Documents	Citations	Avg. citations
USA	393	12081	30.74
England	301	16009	53.19
Sweden	258	15024	58.23
Germany	255	9859	38.66
China	228	3018	10.48
Italy	187	7049	37.70
Switzerland	164	10459	63.77
Spain	120	5247	43.73
Netherlands	104	5438	52.29
France	75	2665	35.53

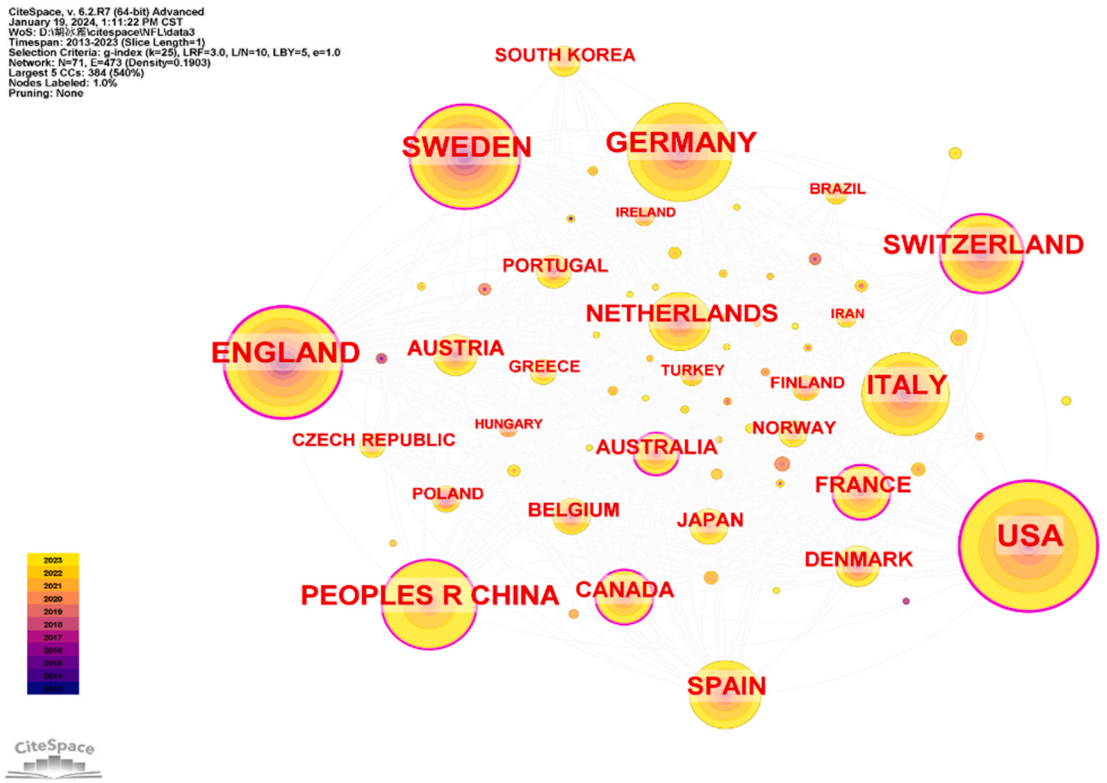

Fig. 3. The relationship between the top countries according to the number of publications.

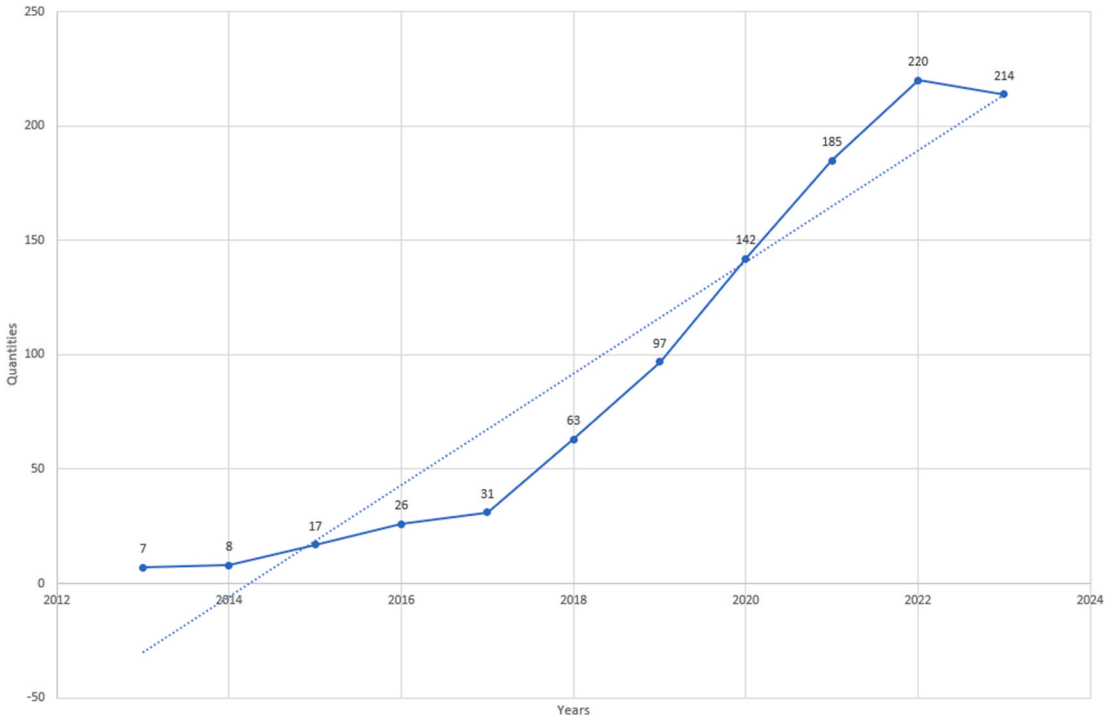

Fig. 4. Annual output of articles from 2013 to 2023.

Table 2
Top 10 institutions by volume of publications.

Insititution	Document	Citation	Avg. citation
University of Gothenburg	195	11510	59.03
Sahlgrenska University Hospital	168	7981	47.51
London's Global University	145	7596	52.39
University College London Institute of Neurology	129	8315	64.46
University of Basel	101	5045	49.95
University of California, San Francisco	58	2649	45.67
Karolinska Institutet	36	2336	64.89
Harvard Medical School	44	1673	38.02
Hong Kong Center for Neurodegenerative Diseases	44	558	12.68
King's College London	32	1898	59.31

3.5. Keyword cluster analysis

Cluster analysis reveals the internal structure of the research field. The keyword network was partitioned into eight clusters based on the strength of keyword co-occurrences (Fig. 8). Each cluster exhibited a high level of homogeneity within its terms. Cluster 0 dedicated to research MS. Cluster 1 primarily focuses on AD which could be attributed to the rising number of patients diagnosed with AD in recent years, while Cluster 2 centers on ALS. Cluster 3 emphasizes that NfL levels change with age. Cluster 4 is dedicated to the study of the serum neurofilament light chain. Because serum testing is less harmful than CSF testing, consequently, testing for NfL in serum is by far the most commonly used test. Cluster 5 focused on alterations in NfL in chemotherapy-induced peripheral neuropathy. Cluster 6 is dedicated to the study of the NfL. Changes in the concentration of NfL in CSF can be used to diagnose a variety of neurological disorders. And Cluster 7 focuses on glial fibrillary acidic protein and NfL as potential biomarkers for neurological diseases such as MS [17]and PD [18].

3.6. Burst word analysis

Fig. 9 cites the fifty keywords with the strongest current sustained bursts. Among them, the strongest outbreaks are " amyotrophic lateral sclerosis " and " csf neurofilament ". In addition, these two words are also the longest duration outbreak words, occupying half of the time in this research area, and are the biggest hotspots for all articles studied from 2013 to 2023. In the last few years, the outbreak words focused on inflammation-related studies.

3.7. Keyword co-occurrence analysis

In order to find out the more important keywords, we limit the minimum number of co-occurring keywords so that the threshold value is 40, and a total of 56 keywords are obtained. As can be seen in Fig. 10, biomarkers as well as NfL is one of the most important keywords. The application of NfL in each disease will be analyzed in the discussion section. The next most frequently occurring keywords at the same time are CSF and NfL diagnosis. The results show that the main focus of current research on NfL is whether it can be used as a biomarker to diagnose the diseases, and the prognosis of the disease development. Among the various methods of detecting NfL, the detection of NfL concentrations in CSF and blood is a commonly used indicator.

4. Discussion

4.1. Analysis of highly cited articles

The most cited article reviews the advancements in neurofilament assay technologies and their role as biomarkers for neuroaxonal damage in various neurological disorders, including MS, neurodegenerative dementia, stroke, traumatic brain injury, ALS, and PD. This is of significant importance for disease monitoring and prognosis assessment [19].

Second most cited article showing that sNfL can predict disease progression in the early asymptomatic stages of familial AD [20]. Also, sNfL can be used to predict the rate of cortical thinning and altered cognitive function. This can be assessed by brief mental status examinations and logical memory tests.

The third most cited article provides a detailed overview of the potential applications of NfL as a biomarker for diagnosis, prognosis, and monitoring of neurological diseases, including its role in MS, AD, ALS, PD, and the development of new immunoassay technologies [20].

The fourth most cited article shows that by examining the association of blood and CSF NfL (cNfL) levels with disease progression and low survival in ALS, which determine that NfL in the blood have prognostic value for ALS [21].

The fifth highly cited article is a 2012 article by Sara Hall, M.D. et al., In 2012, they quantified five CSF biomarkers (α-synuclein, Aβ1-42, T-tau, P-tau, and NfL) simultaneously using a newly developed assay (Luminex) and analyzed them using a conventional enzyme-linked immunoassay. The results suggest that they may reflect pathologic changes in primary neurodegenerative diseases

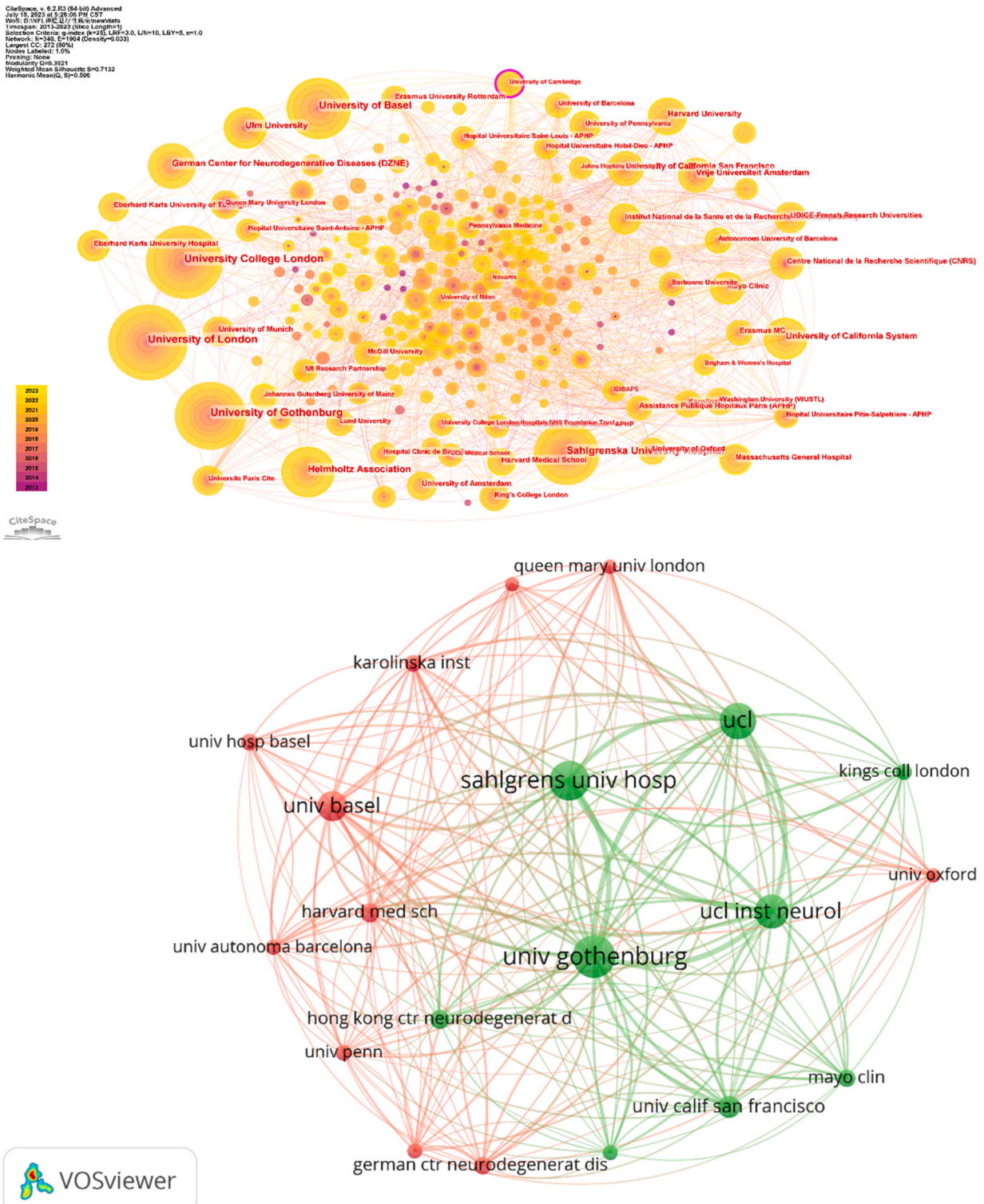

Fig. 5. Institutional Analysis. (a) Co-occurrence relationship diagram. The colour changes from purple to yellow over time. Institutions that are closer to yellow indicate that they have been active in the field in recent years. Node size is positively correlated with the number of articles issued; (b) Co-occurrence relationship graph for institutions with more than 20 annual publications. The thicker the line between any two institutions, the closer the cooperation between them. Green indicates organizations located in Europe, while red indicates organizations located outside European countries.

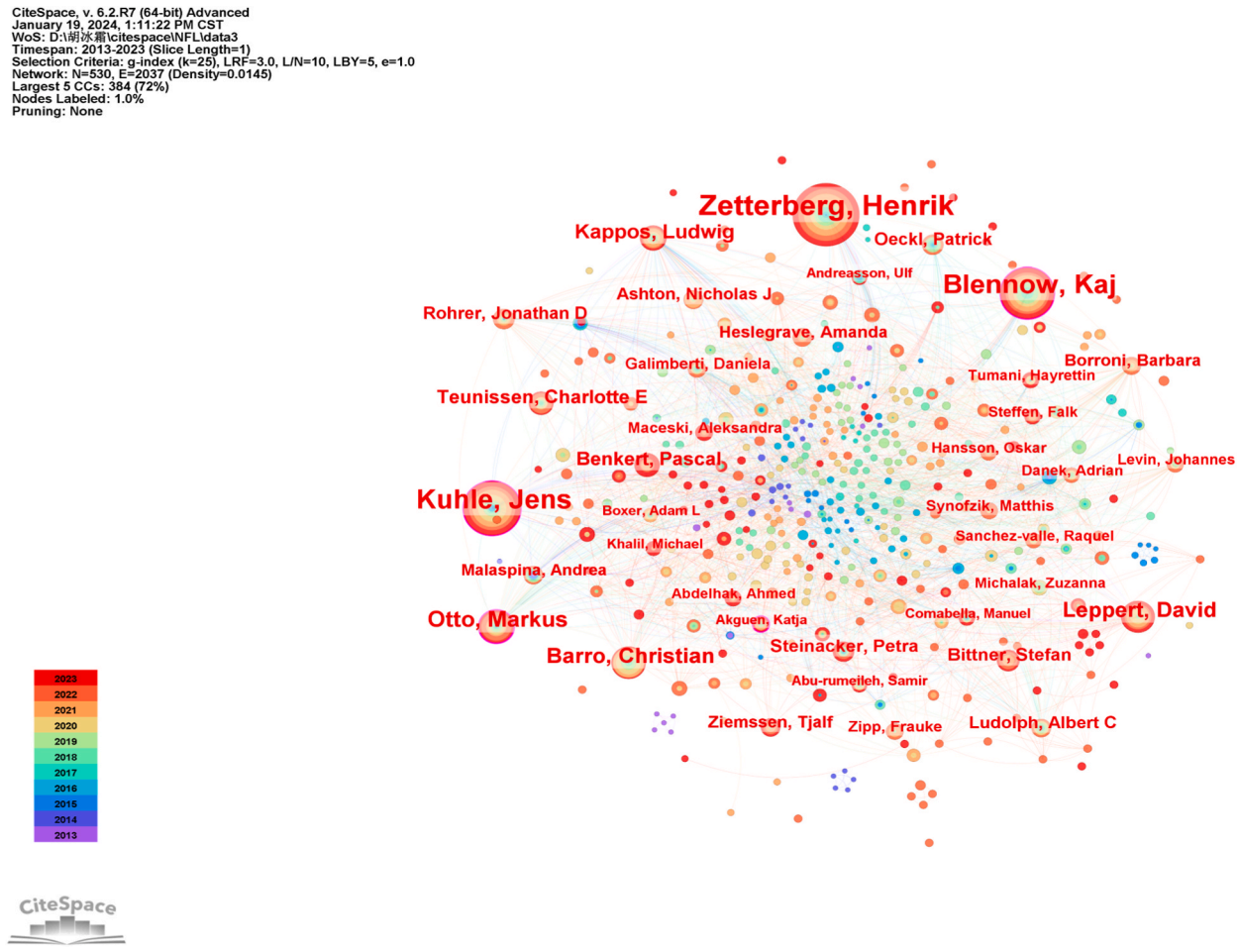

Fig. 6. Author co-occurrence relationship analysis.

Table 3
Top 5 journals by volume of publications.

Journal	Documents	Citations	Avg. citations
neurology	47	3518	74.85
Annals of clinical and translational neurology	47	1333	28.36
Journal of neurology neurosurgery and psychiatry	30	2047	68.23
Multiple sclerosis journal	46	1578	34.30
Journal of neurology	54	1201	22.24

leading to dementia and/or Parkinson's syndrome [22].

Moreover, a highly sensitive electrochemiluminescence-based immunoassay in a study is used to validate the quantification of NfL in blood samples as a source of biofluids that can be easily studied in longitudinal studies and as a potential surrogate for quantifying the effects of neuroprotective medications in clinical trials [10]. A study by Magnus Gisslén et al. developed an ultrasensitive Simoa immunoassay using a cross-sectional design, demonstrating that plasma NfL has the potential to be a good indicator of CNS damage in HIV infection and is likely to be equally applicable in other neurodegenerative disorders, which may be helpful for clinical and research purposes [23]. Another research used the ultrasensitive Simoa method to measure blood NfL concentrations to determine blood NfL protein. Differences in CSF and serum concentrations can be used to differentiate between PD and APD [24]. These are the basis for more in-depth studies of NfL.

4.2. Evolution of hotspots, knowledge structures and emerging themes

In recent years, research in this area has been aimed at demonstrating the correlation between neurodegenerative diseases and NfL,

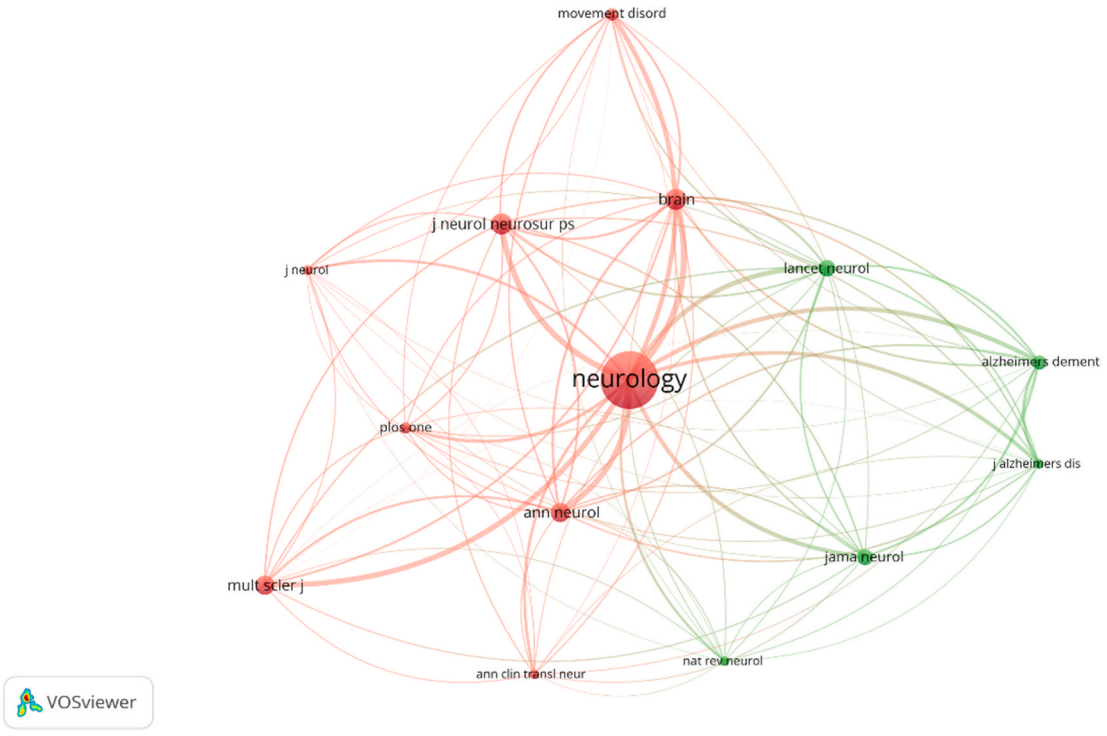

Fig. 7. Visualization of co-citation analysis clustering by journals with more than 1000 total citations to published papers. Nodes represent journals and the size of the node is determined by the number of co-citations for that journal. Green indicates: journals that are more focused on Alzheimer's-related research, while red indicates: journals that are more skewed toward research on other diseases of the nervous system.

and the use of cNfL values has improved the diagnostic certainty of neurologists [25]. Elevated NfL levels are a common feature of neurodegenerative dementia. The field is centered around the use of cNfL concentrations to diagnose various brain disorders and their clinical manifestations, as well as to hypothesize prognosis. In several neurodegenerative dementias, NfL levels in CSF are elevated [26].Among them, MS and ALS have been the main subjects of analysis, but in recent years, more and more studies have focused on the value of NfL in AD. The use of NfL as a biomarker in various diseases will be specifically analyzed below.

4.2.1. Alzheimer's disease

AD is a neurodegenerative disorder with cognitive deficits and progressive neuroatrophy. Nonphysiological accumulation of amyloid-β peptides in extracellular plaques and aggregation of hyperphosphorylated tau proteins in intracellular neurofibrillary tangles constitute the neuropathological hallmarks of AD in the human brain.

In 2014–present, research terms increasingly covered AD, showing AD may hold significant transitive implications in this phase. Plasma NfL/Abeta1-42 could serve as a plasma-based non-invasive biomarker, holding significant value for early diagnosis and disease progression monitoring in the AD spectrum [27,28].

There are significant differences in plasma levels of NfL in patients with AD compared to normal controls, and NfL has also been shown to be useful in predicting disease progression [29]. Concluded that the onset of early clinical symptoms of AD is associated with a sudden increase in sNfL. This is consistent with previous studies [30]. Elevated cNfL levels were found by Skillback et al. [31]. However, because cNfL levels increase with age, not only in patients with many neurodegenerative diseases, including AD, but also in healthy individuals. Therefore, when making a differential diagnosis of AD, the examiner should use the age-specific cNfL reference value.

An association between dominantly inherited AD and brain NfL levels has been demonstrated, and NfL is elevated in the pre-symptomatic phase of familial AD. Moreover, measurement of the annual rate of change in NfL using serial sNfL can distinguish between chromosomal dominant AD mutation carriers and non-mutation carriers earlier than estimated symptom onset, compared to measurement at a single time point. Because the use of continuous NfL measurements can be differentiated as early as 16 years before symptom onset, whereas the use of absolute NfL levels measured at a single point in time would be nearly a decade late [32,33]. However, whether this phenomenon exists in sporadic AD has not been proven confirmed. Up to now, most of the data obtained is at the population level, and more in-depth analyses and further longitudinal studies with large populations are needed to explain NfL concentrations at the individual level.

In recent years, the hotspot of the NfL field has been in the study of cognitively impaired disorders such as AD and other related cognitive disorders, and there has been an increasing interest in molecular imaging of the brain, such as imaging related to neuro-inflammation in microglia and macrophages [34], and neurodegeneration related to tau proteins and Lewy bodies [35], in addition to

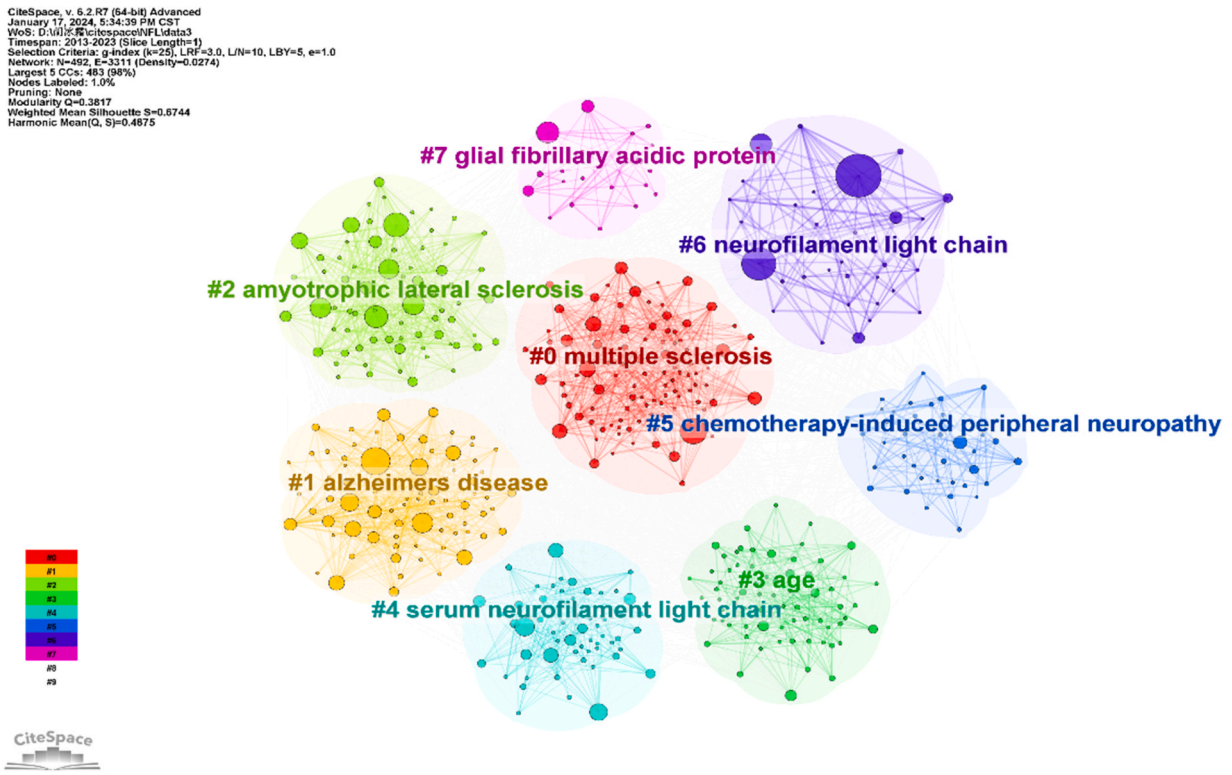

Fig. 8. Clustering visualization for keyword co-occurrence analysis. Citespace classifies keywords into eight different clusters based on their internal structure. Each cluster has a different meaning it represents.

Top 15 Keywords with the Strongest Citation Bursts

Keywords	Year	Strength	Begin	End	2013 - 2023
amyotrophic lateral sclerosis	2013	6.11	2013	2018	
csf neurofilament	2015	5.75	2015	2019	
neurodegenerative diseases	2016	5.63	2016	2018	
heavy chain	2016	5.1	2016	2018	
progressive supranuclear palsy	2015	5.09	2015	2020	
cerebrospinal fluid	2013	5.03	2016	2018	
disease activity	2017	5	2019	2021	
clinically isolated syndrome	2013	4.8	2017	2019	
csf	2013	4.71	2017	2019	
frontotemporal lobar degeneration	2017	4.54	2017	2018	
serum neurofilament	2017	3.91	2017	2020	
markers	2015	3.81	2015	2017	
brain atrophy	2019	3.76	2019	2020	
inflammation	2017	3.71	2019	2021	
light chain	2016	3.55	2018	2020	

Fig. 9. Burst word analysis. The red bars indicate the duration of the bursts, reflecting frequently cited keywords, and conversely, the blue bars indicate infrequently cited keywords.

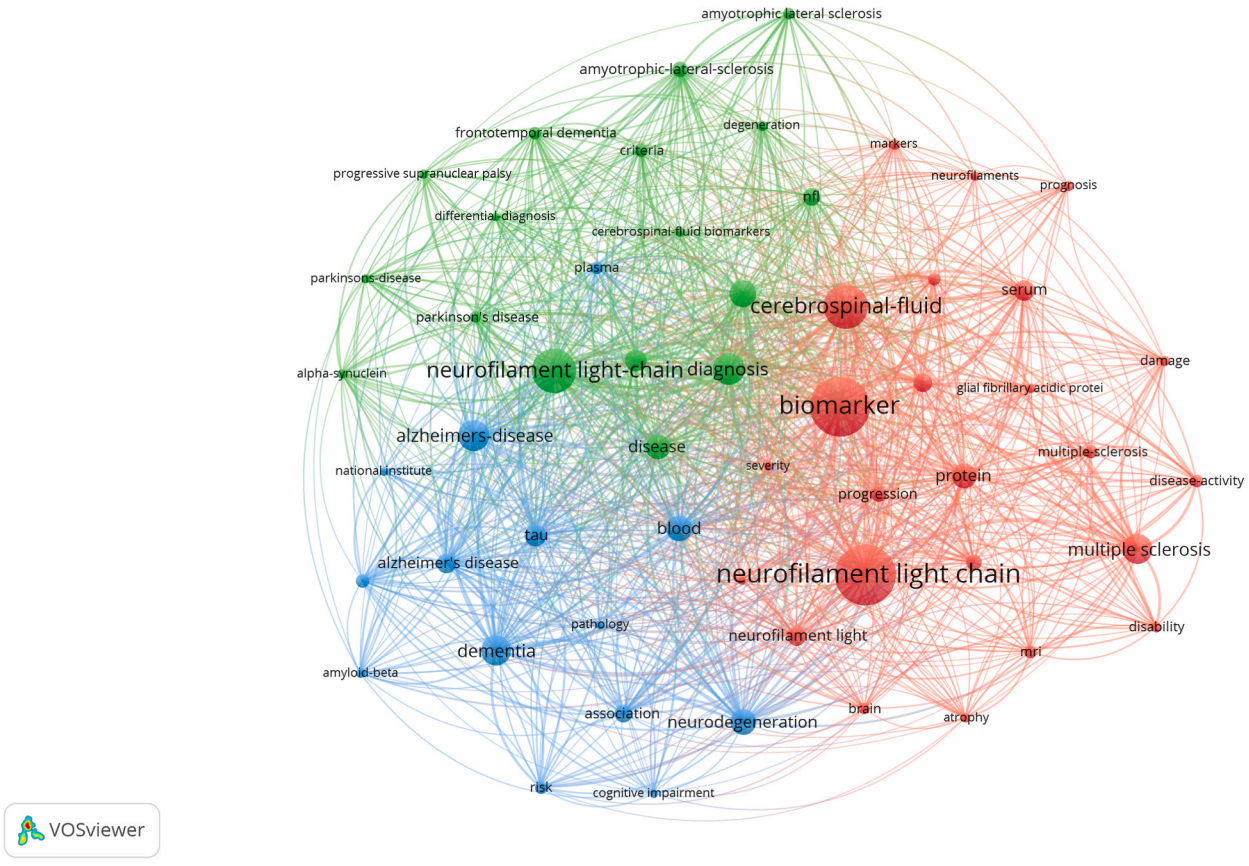

Fig. 10. Keyword co-occurrence analysis. The larger the diameter of the circle, the more frequent the co-occurrence and the more important the keyword. The blue portion indicates the application of NfL in Alzheimer's disease, the red color indicates that NfL can be applied as a biomarker, and the green color represents the application of NfL in a variety of diseases.

biomarkers.

4.2.2. Amyotrophic lateral sclerosis

In contrast to AD, ALS still lacks specific neurochemical biomarkers that reflect in vitro neuropathology. However, considerable progress has been made in the last decade in studying NfL as blood biomarkers of neurological diseases.

NfL can be used as a biomarker for the detection of ALS. ALS is characterized by relatively rapid degeneration of motor neurons that have large myelinated axons, i.e., contain large numbers of neurofilaments. This is the main reason for the substantially higher concentration of NfL in the CSF in ALS compared to other common neurodegenerative diseases [36]. Besides, NfL has been used as a potential biomarker along with another potential biomarker called Threshold-tracking Short-Interval Cortical Inhibition (T-SICI), and together they can be effective in differentiating between ALS patients and ALS mimicry [37].

Neurofilament levels in CSF can be measured by conventional ELISA [9]. Semi-sensitive electrochemiluminescence detection is the first method to measure changes in peripheral blood concentrations in samples from ALS patients. Data from several studies have shown that cNfL levels in ALS are increased several-fold compared to healthy controls [38,39]. Thus, NfL can be used to predict the onset of clinical manifestations of ALS, whereas elevated NfL levels mark the onset of clinical manifestations of ALS. In addition, because NfL correlates with the rate of disease progression and is negatively correlated with survival, plasma NfL can also be used to estimate the short-term and long-term prognosis of ALS [21,40–44]. However, there is no evidence of a difference in survival between patients with hereditary ALS and those with sporadic ALS [41].

Study confirmed a significant difference in cNfL levels between the two diseases by measuring and comparing cNfL levels in patients with ALS and patients with ALS mimetic disease, which makes NfL useful for differentiating between mimetic diseases and may be worth considering its introduction into diagnostic criteria [45]. In addition, plasma NfL levels can be used to differentiate between clinical and genetic ALS subgroups [46]. Familial ALS is defined as the inheritance of ALS and related syndromes (e.g., FTD) in family members, with approximately 70 % of familial cases having mutations in known ALS genes (SOD1, C9orf72, or VAPB genes). Sporadic ALS refers to patients with no family history of ALS. Only about 15 % of sporadic ALS cases are known to be due to " private " disease-causing mutations in known ALS genes that are restricted to a single individual, whereas the mechanism of etiology of the rest is not known [47]. Higher levels of NfL in patients with upper motor neuron involvement in ALS subtypes [41].

Although almost all studies of ALS and NfL agree that changes in NfL concentrations are not related to gender[41,48].However, some studies have found that female ALS patients have higher concentrations of NfL in their blood compared to men [21,49,50]. In contrast to other neurological disorders, most studies have concluded that there is no correlation between CSF and sNfL levels and age in patients with ALS [39,43,48,51]. However, some studies have reported a weak correlation between CSF or sNfL levels and age in ALS [10,49]. The longitudinal evolution of NfL concentrations is stable [52,53].

4.2.3. Multiple sclerosis

In ALS, NfL in blood or CSF has been shown to be a useful indicator for diagnosis, prediction of ALS relapses, objective prediction of gadolinium-enhancing lesions and T2 lesion progression, prediction of exacerbation and clinical changes in multiple sclerosis, prediction of disease progression unrelated to relapsing activity, and assessment of the effectiveness of disease-modifying therapies [7,54,55]. Besides, elevated NfL concentrations in CSF and blood were associated with increased MS recurrence, disability worsening, MRI disease activity, and brain volume loss [16,56]. This suggests a potential clinical use as evidence for monitoring disease progression, disease activity and treatment efficacy [57]. Moreover, NfL has an advantage in predicting disease activity at 2 years, as evidenced by CNfL's ability to predict short-term disease activity in the form of contrast-enhancing lesions, recurrence, or both [58]. In studies of patients with MS, it has been found that the closer the patient is to clinical onset, the higher the sNfL level. The stage of onset itself is also associated with significantly higher levels of sNfL [59]. This suggests that NfL is not only a biomarker of neurodegeneration but also plays a crucial role in the pathogenesis of MS [60]. At the same time, it has been found that plasma NfL showed stronger predictive power than cNfL, i.e., serum NfL correlated more strongly with MS severity outcomes than did cNfL [58,61].

The most studied type in this field is the use of NfL in relapsing-remitting multiple sclerosis. And, in a twenty-year follow-up study, NfL levels were found to be significantly higher in the aggressive RRMS (aRRMS) group than in the benign RRMS (bRRMS) group. NfL was able to differentiate between aRRMS and bRRMS [62].

In addition, the clinical application of blood NfL levels and MRI measurements has been found to be closely correlated in the studies. Examining blood NfL levels is more suitable for real-time monitoring of disease activity and drug response than MRI, and it is less burdensome for patients. NfL is more valuable than traditional MRI measurements. This is because changes in brain atrophy on MRI represent tissue damage that has already occurred, whereas NfL is highly predictive of future brain atrophy [63].

Recent studies have revealed the presence of a unique immunogenic cluster, i.e., a characteristic protein motif described by the regular expression P-(SA)-x-(SGA)-R–(SN)–(LRKH) (" IC motif ") in serum samples both before and after the onset of MS. The starting proline is the most conserved structure, and its characteristic arginine-serine repeat sequence is highly representative of the enriched peptides. MS patients screened according to this protein motif signature had significantly higher sNfL levels than other MS patients, and the difference in sNfL levels remained constant across serum collection time points [64].

4.2.4. Parkinson's disease

A study confirmed that CSF levels of NfL are elevated in APD and that the observed diagnostic accuracy (AUC, 0.93) of NfL is sufficiently high to be clinically relevant. NfL facilitates differentiation between different types of PD (i.e, PD vs APD) [65]. In addition, there are promising studies showing that CSF levels in NfL can be used to differentiate PD from multiple system atrophy, progressive supranuclear palsy and corticobasal degeneration [65–68].

4.2.5. Huntington's disease

Furthermore, cNfL levels were significantly higher in HD subjects and correlated with scores on the Unified Huntington's Chorea Rating Scale Total Functional Capacity Assessment [69]. However, to date, there is no evidence to illustrate the potential of cNfL levels to serve as a biomarker of HD disease activity, and further research is needed in this regard.

4.3. Factors affecting the NfL

Most of the NfL in the blood comes from the CNS [7]. Serum or plasma NfL levels in healthy individuals are only about 2.5 % of CSF levels. Detection of blood and plasma NfL levels in the same individual reveals that sNfL is slightly higher than that in plasma [70]. This suggests that different types of assays will affect the level of NfL, and therefore a single specimen should be selected whenever possible for research and clinical applications.

NfL is used as a blood biomarker for neural axonal injury and neurodegenerative diseases, and there are several high-throughput automated systems of NfL immunoassays under development, for example, there are four NfL assays including Quanterix Simoa, Roche Elecsys, Siemens Healthineers AtellicaIM, and Fujirebio Lumipulse are available for obtaining NfL concentrations in plasma, and there is a strong correlation between these methods, but there is also a significant proportionality bias, in particular the Roche Elecsys assay has significantly lower NfL concentrations than the other methods [71].

It has been found that synaptic remodeling during sleep may alter NfL kinetics, resulting in a disparity between morning and evening measurement levels [72]. In addition, gender also affects NfL. According to the survey, healthy women have lower cNfL levels than healthy men [73]. Interestingly, Thouvenot et al. found that this pattern did not apply to ALS patients [74]. In ALS patients, this is even the opposite. This suggests that gender-specific reference values are needed for the NfL.

Age also affects changes in NfL levels. There is a correlation between NfL and patient age, which means that age-specific reference values may be needed, sNfL levels in adults are positively correlated with age and increase annually with age [73].

However, the variation in NfL levels in children is not homogeneous: although newborns have high levels of NfL [75], children's NfL levels reach their lowest levels at about 10–15 years of age, which may lead to low levels of NfL in older children. After 15 years of

age, i.e., after the pubertal stage, the NfL increases linearly until about 60 years of age. NfL levels show a nonlinear and rapid increase after age 60 [76,77]. In neurological disorders with significantly increased NfL levels, such as ALS, FTD, HD, and APD, NfL shows a strong correlation with age, which may be due to the fact that the neuropathologic process masks the age correlation. In addition, race [78], renal function [79], disease duration and severity [73] may also affect cNfL levels, which are indicative of NfL proteins in CSF that reflect neuronal damage. Measuring the NfL while considering other comorbidities interfering with measurement is necessary.

4.4. Future research directions

Although NfL is now well understood, some questions remain to be addressed. First, studies have shown that plasma NfL helps distinguish between ongoing active neuronal injury and neurologic or cognitive symptoms associated with sequelae of CNS injury occurring prior to the initiation of treatment, known as inactive disease, but this issue requires further direct research [80]. However, it is unclear which pathologic processes in the CNS can be adequately detected by peripheral measurements and whether plasma biomarkers are equally applicable in the clinical and preclinical phases.

In addition, despite the emergence of a variety of more sensitive detection technologies in the clinic, there are still issues that need to be addressed for the full implementation of NfL in clinical practice. First, there are limitations in accurately detecting very low levels of target analytes. Second, because measurement methods vary greatly from laboratory to laboratory, there is a need to standardize blood NfL measurements globally. The quantitative values of NfL observed in the large number of studies covered in this field vary widely and are not standardized, which may lead to misinterpretation. In addition, we should also analyze in greater depth which clinical factors influence the level of NfL in order to establish a reliable threshold value. Standardized tests and well-validated thresholds will be key to the routine implementation of NfL in clinical practice. What's more, previous studies have focused almost exclusively on adults, with an emphasis on the elderly. But children are also susceptible to genetic or congenital neurological disorders due to their population specificities, such as neonatal brain injury due to asphyxia; spinal muscular atrophy, a common fatal autosomal recessive disorder in infants and young children, and traumatic brain injury, CNS tumors, autoimmune encephalitis, and many other causes of pediatric epilepsy and so on. Therefore, it is hoped that future research in this field will focus more on children. Research among young people deserves equal attention.

Furthermore, the phenomenon that cNfL increases with age has been clearly defined in earlier large studies [81]. However, the regulatory mechanism for changes in the concentration of NfL is not clear. It may be due to passive release after axonal injury, increased protein expression or decreased protein clearance, or a combination of both. Therefore, this issue requires further studies by researchers, which may help in practical clinical applications. Meanwhile, in AD, for example, cNfL levels are significantly increased in patients 1–2 years prior to the onset of overt dementia symptoms, but data from this study have been overlooked. Therefore, data that can fully confirm long-term observations prior to diagnosis is warranted. Repeated measurements may be needed in clinical trials to track the rate of change in axonal degeneration over time. The next steps in this field should focus on long-term follow-up of large and unscreened healthy populations until clinical manifestations of neurological disease may occur. In addition, patients with disease regression should also be subjected to more disease-specific and in-depth studies to better investigate the process of neurological disease transition. In addition, much of the current research in this area focuses on cross-sectional studies and lacks important longitudinal studies. Therefore, more longitudinal studies are needed.

4.5. Limitations of the study

To the best of our knowledge, this is the first bibliometric study of related studies, but there are still shortcomings. The data was obtained from Web of Science, there may be incomplete coverage of the data.

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Data availability

The datasets generated during and/or analyzed during the current study are available in the Web of Science.

Ethics approval

No ethical implications.

Consent to participate

Not applicable.

Consent for publication

Not applicable.

CRediT authorship contribution statement

Zhengxi Song: Writing – original draft, Visualization. **Shan Zhang:** Writing – original draft, Visualization, Data curation. **HongYu Pan:** Writing – original draft, Visualization. **Bingshuang Hu:** Writing – original draft, Visualization, Conceptualization. **XinLian Liu:** Supervision, Funding acquisition. **Jia Cui:** Supervision, Funding acquisition. **LuShun Zhang:** Supervision, Funding acquisition.

Declaration of competing interest

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

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e34720.

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