Future Integrative Medicine **2023** vol. 000(000) | 000–000 Epub
DOI: 10.14218/FIM.2023.00019

Systematic Review

Visual Analysis of Research Hotspots in Amyotrophic Lateral Sclerosis based on Bibliometrics

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Received: April 19, 2023 | **Revised:** June 20, 2023 | **Accepted:** July 25, 2023 | **Published online:** August 14, 2023

Abstract

Background and objectives: Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease that is often diagnosed when affected individuals die with respiratory failure. Currently, there are few bibliometrics studies on ALS.

Methods: In this study, a comprehensive literature search using the PubMed, WangFang, China National Knowledge Infrastructure, and Chinese Science and Technology Periodical databases was conducted. The Core Collection database for scientific output related to ALS from 1990 to 2022 was also searched. The retrieved dataset was analyzed using.

Results: Bibliometrix. A total of 12,450 articles published since 1990 were retrieved, and 243 articles were included in this study. Thirty-two countries contributed to ALS research, among which Italy had the dominant position with the highest number of publications. In addition, keyword co-occurrence was analyzed. As the three indirect subjects of this article, the sources, affiliations, as well as authors of the study were included in the analysis.

Conclusion: In recent years, ALS research has made some progress in terms of elucidating the mechanism of the disease and providing clinical treatment, but the results are concentrated in the United States and European countries. For more complicated research results, critical analysis must be performed.

Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative condition, featuring the loss of motor neurons in the cord, cortex, cortical spine, and brainstem. The incidence of ALS is 1.75 (1.55–1.96) per 100,000 people,[1] 5–10% of cases are familial and hereditary, and 90–95% of cases are sporadic. As no effective therapy exists, those diagnosed usually die within 3–5 years after symptom onset.[2] Although the interaction between endogenous and exogenous factors is believed to be involved in the development of the disease, the underlying cause of ALS remains unknown[3] and is likely due to the heterogeneous nature of ALS.[4] The real complexity of understanding ALS may be divided into two parts. There are many hypotheses regarding the mechanism of ALS pathogenesis (the first part), which mainly includes some genetic (most cases are caused by variants of the SOD1, C9orf72, and TARDBP genes,[5] environmental or developmental factors, as well as RNA/protein mishandling, excitotoxicity, or oxidative stress.[6,7] The authenticity of various treatments proposed is difficult to distinguish (the second part). According to preliminary studies, there are currently about 20 therapeutic methods used in clinical practice, including synthetic small-molecule drug therapy[8] that has been mainstream for a long time, and emerging therapies such as stem cell therapy[9] and traditional Chinese medicine therapy.[10] The oral drug riluzole, the only approved disease-modifying treatment for ALS, also has the following shortcomings: it only prolongs the life of patients by 2–3 months,[11] it is expensive, and it causes adverse reactions such as nausea and fatigue. Therefore, it is urgent to settle some issues and allocate more resources to ALS research.[12] Identifying novel therapeutic targets,[13] trying to explore more availably therapies, and conducting holistic and objective critical analyses are important. The current gold-standard measure of ALS progression is the Functional Rating Scale-Revised;[14] of course, other methods such as the weakness scale as the silver index to measure many problems can also be used. This review had the following aims: (1) to introduce the current global ALS research trends, and (2) to summarize the development of related research.

Keywords: Amyotrophic lateral sclerosis; Bibliometrics; Collaboration; Trending; Research type; Data tendency.

Abbreviations: ALS, amyotrophic lateral sclerosis; RCT, randomized controlled trials; TCM, traditional Chinese medicine.

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How to cite this article: Yang X, Wang T. Visual Analysis of Research Hotspots in Amyotrophic Lateral Sclerosis based on Bibliometrics. *Future Integr Med* 2023;000(000):000–000. doi: 10.14218/FIM.2023.00019.

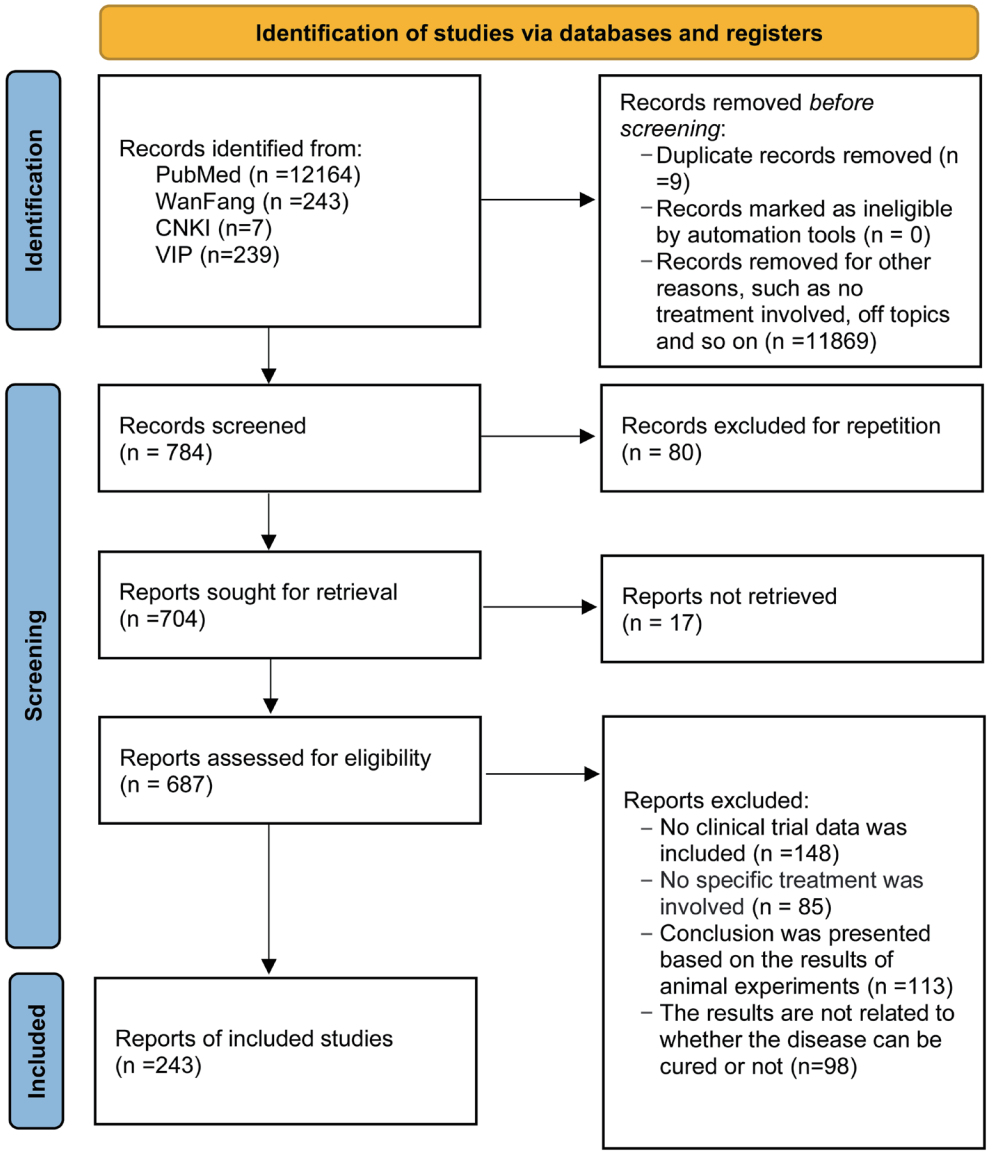

Fig. 1. Flow diagram of the articles included in this study.

Methods

Data collection

The papers written in English in this study were derived from PubMed, with 12,163 articles in total. The Chinese articles were retrieved from the WangFang, China National Knowledge Infrastructure, and Chinese Science and Technology Periodical databases, which are three representative databases in China, covering journals, conference minutes, papers, academic results, and academic conference papers, with 287 articles in total. The search keywords were "MeSH (ALS, treatment)". To investigate the trends in the treatment of ALS in the past 30 years, the search year was set from 1990 to 2022. Citation data were from Google Scholar, obtained through the Publish or Perish software, and matched with PubMed articles. According to the type of paper, the article title and abstract were retrieved. Citations based on animal experiments, not containing clinical cases, or not related to the research direction were excluded. After screening, 243 full-text articles were deemed eligible for this study, as illustrated in Figure 1.

Research methods

A total of 17 treatments mentioned in 243 articles were classified and counted, and each treatment was used for the trend study. At the same time, the research methods were statistically analyzed, including randomized controlled trials (RCTs), case studies, and cohort studies. We also used Bibliometrix to analyze affiliation, author, country, source, word, and annual production of the literature, and a series of visualization maps showing the current mainstream research hotspots and research trends were simultaneously generated. Bibliometrix is an open-source tool for quantitative research in scientometrics and bibliometrics that includes all the main bibliometric methods of analysis. With Biblioshiny, a Shiny web app, Bibliometrix has become very easy to use, even for those who have no coding skills.

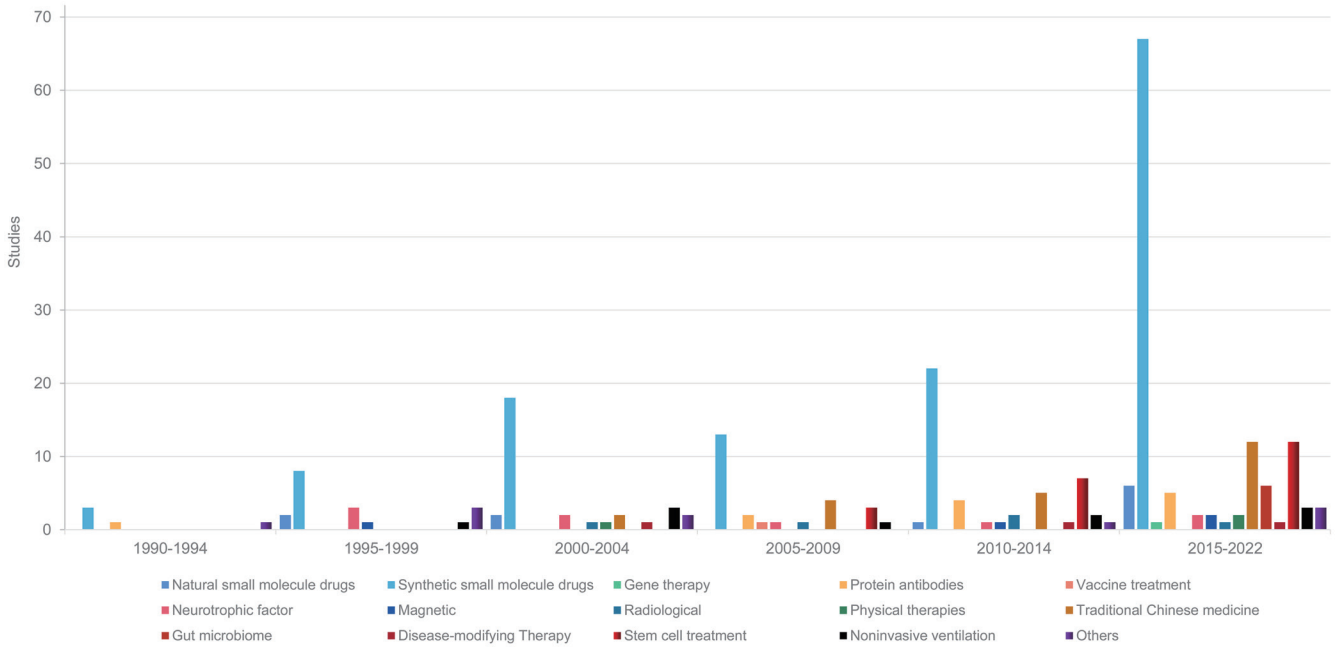

Fig. 2. ALS treatment trends of the included studies.

Results

Flow chart

The final 243 articles included in this study, all related to the results of clinical trials, notably contributed to our conclusions, such as which drugs might actually work.

Development trend of research hotpots

After analyzing the included papers, the ALS treatments mentioned in the 243 references were divided into 15 groups, including natural small-molecule drugs, synthetic small-molecule drugs, gene therapy, protein therapy, antibody therapy, neurotrophic factor therapy, radiotherapy, repetitive transcranial stimulation, exercise therapy, and traditional Chinese medicine (covering Chinese herbal medicine, acupuncture, mosibution, massage, and a collection of treatments from Japan, Korea, and India), stem-cell therapy, gene-modified therapy, gut microbiota, noninvasive ventilation, and others (covering cerebrospinal fluid, polyethylene glycol, osteopathic manipulation treatment, hyperbaric oxygen therapy, etc.). A five-year cycle trend chart is presented in Figure 2. According to the figure, the main points can be summarized as follows: (1) From 1990 to 2022, the synthesis of small-molecule drugs has been the top stream of research and has risen; at the same time, new small-molecule drugs have been discovered and developed for clinical treatment. There are many kinds of small-molecule drugs, and their efficacies are different; thus, objective identification and analysis are required. (2) Since 2005, research on stem cell therapy and traditional Chinese medicine has gradually grabbed the public's attention, and these two methods have become the second and third most common research topics from 2015 to 2022, proving that with the deepening of the research on the pathogenesis of ALS, a new perspective for finding real solutions to the problem has been reached. However, the number of studies needs to be further increased to ensure the rigor of the results. (3) The remaining therapies have been investigated at the same level but in a small scope, so further clinical trials are needed to ensure their efficacy.

Development trend of research types

The research methods were divided into three types: RCT, case study, and cohort study. Statistical analysis revealed that RCT studies accounted for the highest proportion of all literature reports on ALS. The references were also categorized into western medicine-based, traditional Chinese medicine-based, drug treatment-based, nondrug treatment-based, and synthetic small molecule drug treatment-based categories. In order to intuitively see the proportion of each research method, we made pie charts (Fig. 3).

At the same time, by analyzing the trend chart of the number of research types through the line chart (Fig. 4), it was found that each method had a rapid growth period, especially RCT. With the continuous progress of technology, our understanding of ALS is deepening, and the research on the treatment of ALS is developing rapidly as well. Although the comparability between the RCT groups was high and the RCT groups had good internal validity, the external validity of RCTs is a drawback. Due to the strict inclusion and exclusion criteria of RCTs, the study subjects had a good homogeneity. However, the results may not be extrapolated to practice. Therefore, the results of RCTs also need to be confirmed by more case studies and cohort studies.

Bibliometric analysis

Number of published periodical articles

The annual number of publications fluctuated from 1991 to 2022, but it showed an overall growing trend, with the largest number of publications in 2020. This marks the continuous development of ALS treatment methods, with the field being more deeply understood and the research results becoming increasingly fruitful (Fig. 5).

Countries

The countries and areas of publication of the references was analyzed, and the results are shown in Figure 6. The top five coun-

Type of therapy	Type of research	Number of articles
Total	RCT	132
	Case	86
	Cohort	36
Based on traditional Chinese medicine	RCT	8
	Case	7
	Cohort	8
Based on western medicine	RCT	124
	Case	78
	Cohort	28
Medication-based treatment	RCT	86
	Case	33
	Cohort	21
Based on nonpharmacologic treatment	RCT	45
	Case	47
	Cohort	9
Based on synthetic small molecule drugs	RCT	79
	Case	32
	Cohort	20

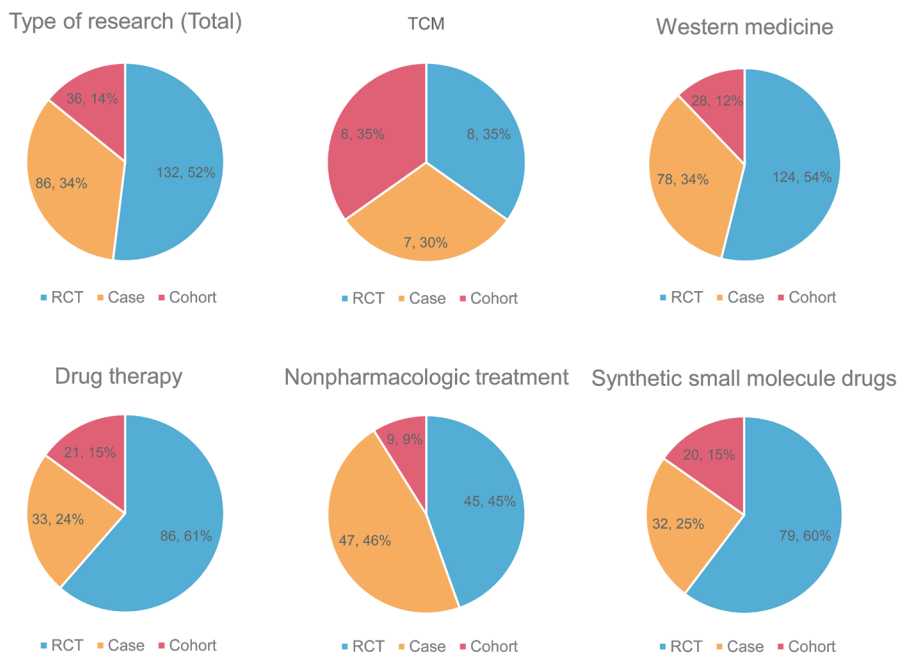

Fig. 3. Research methods of the included studies.

tries and areas were Italy (n = 219, 90.12%), the USA (n = 205, 84.36%), Japan (n = 173, 71.19%), Germany (n = 106, 43.62%), and Spain (n = 75, 30.86%), with Italy leading the way. It can be seen from Figure 6 that the research achievements are mainly from the USA and Europe, since the technology is relatively mature there. At the same time, we found that the frequent cooperation between the USA and Europe is one of the reasons for their rapid development in this field. In contrast, some countries

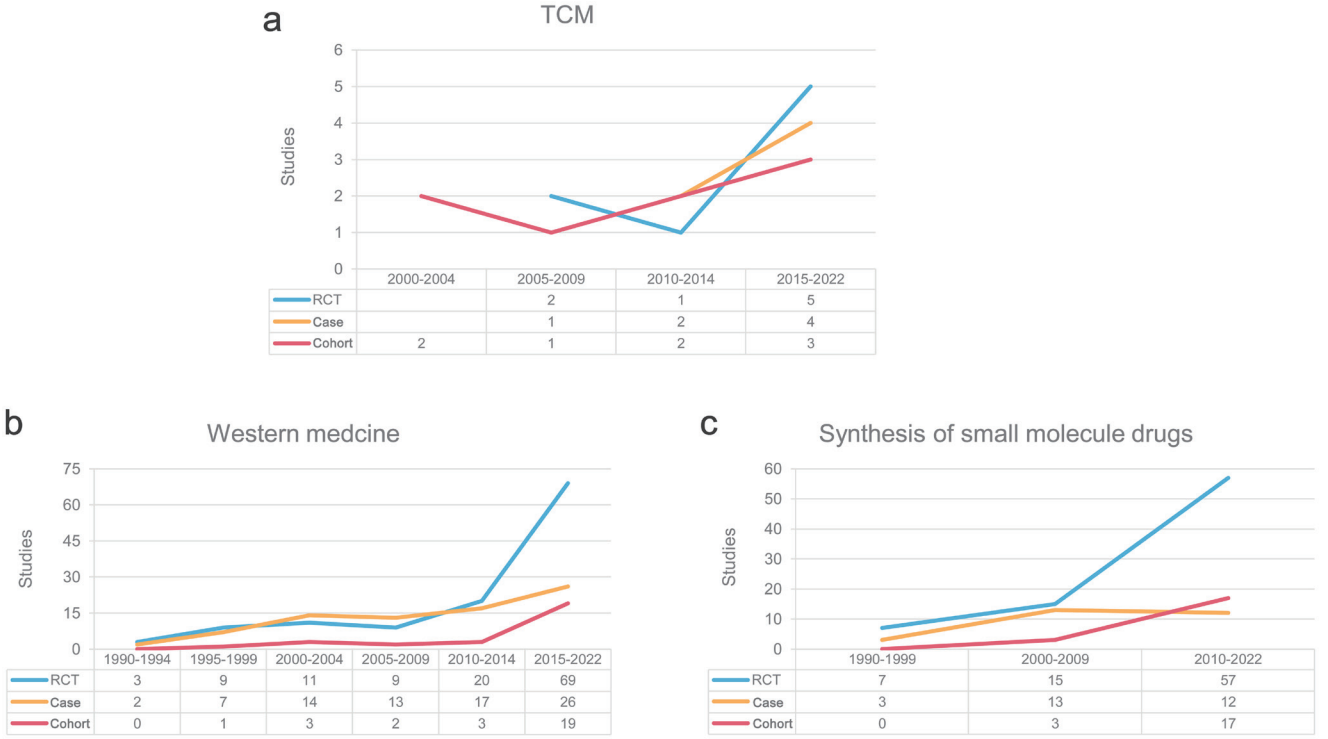

Fig. 4. Research types of the included studies. (a) TCM; (b) Western medicine; (c) synthesis of small molecule drugs. RCT, randomized controlled trials; TCM, traditional Chinese medicine.

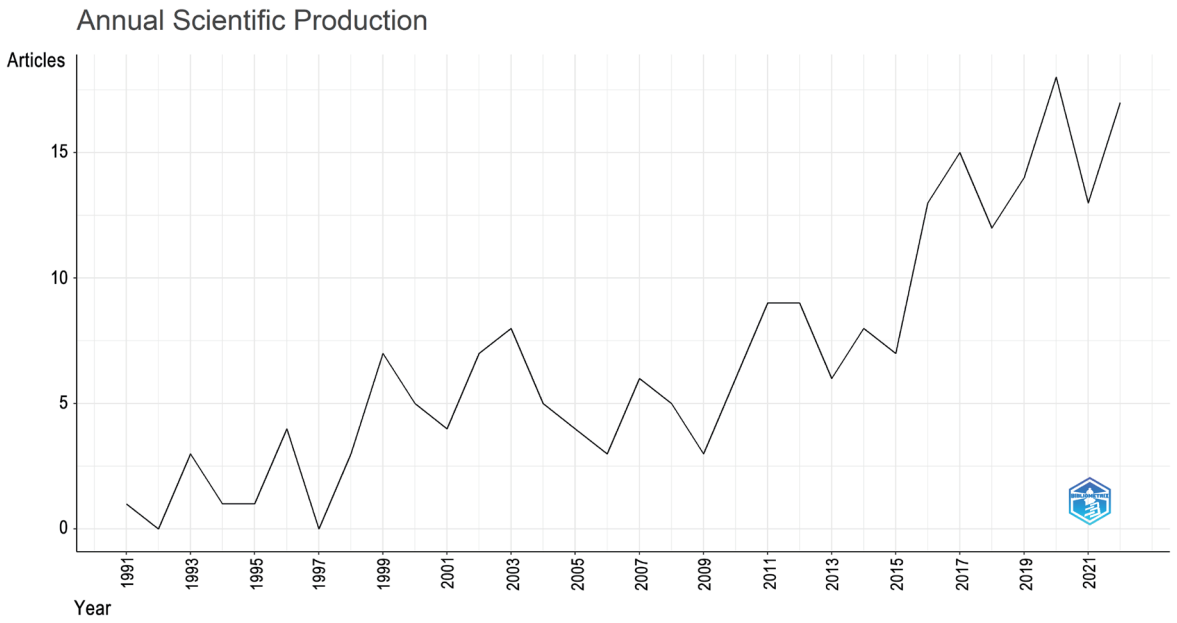

Fig. 5. Annual scientific production of amyotrophic lateral sclerosis studies.

in Asia have less cooperation with other countries. China has only conducted individual cooperation with European countries, and the results are usually from domestic research. Moreover, there is a problem with the data processing as the sum of publications reported in the top countries (Italy, USA, Japan, Germany, and Spain) is 778, which is much greater than the total of 243 documents that are included and analyzed in the current study. The reason for this discrepancy may be the joint publication of a journal article by several countries.

Institutions

The publishing institutions of the references were analyzed (Fig. 7), and the 10 most closely related institutions were excluded. Among them, Harvard Medical School published 70 papers, accounting for about a quarter of the references, and the remaining institutions published 20–30 papers. It can be seen that universities or research

Fig. 6. Map of countries and areas with scientific production and collaboration of amyotrophic lateral sclerosis studies.

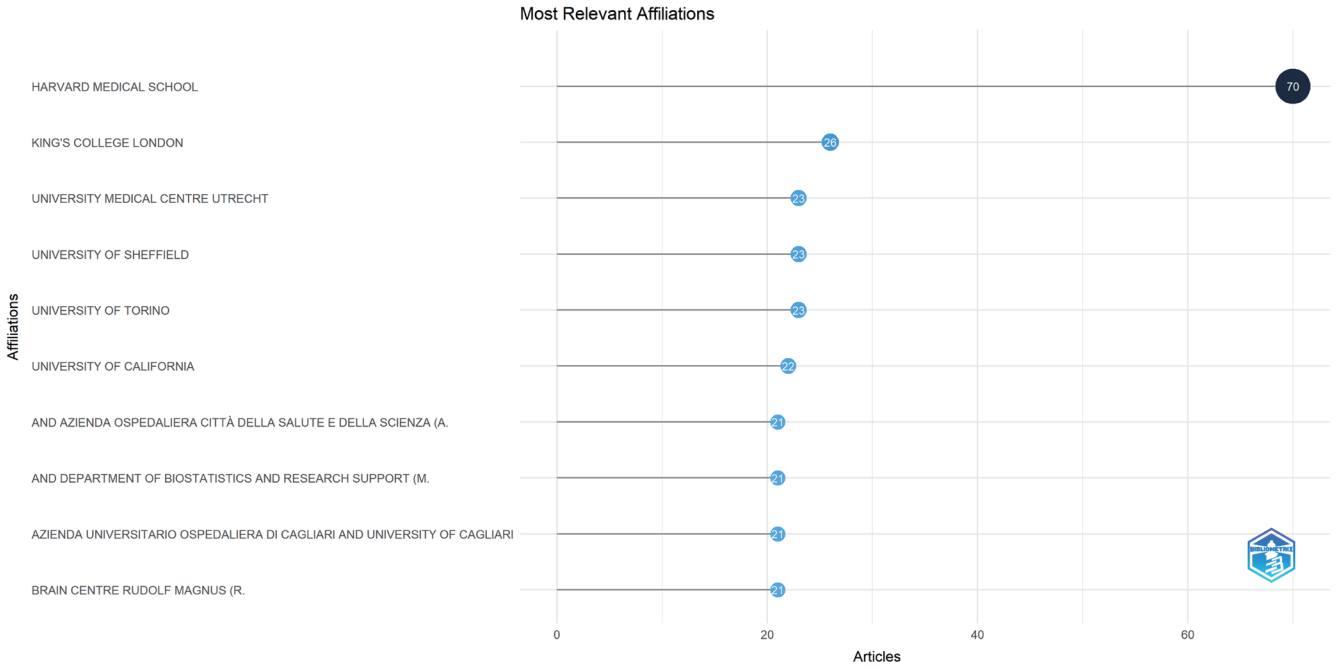

Fig. 7. Most relevant institutions of amyotrophic lateral sclerosis studies.

institutions were responsible for the publications. Though there are many research institutions, the results are relatively concentrated.

Sources

The journals of the references were analyzed, and the 10 most closely related sources are listed in Figure 8. The top three journals were *Amyotrophic Lateral Sclerosis & Frontotemporal Deg* (17 papers, accounting for 6.996%), *The Cochrane Database of Systematic Reviews* (14 papers, accounting for 5.761%), and *Muscle & Nerve* (12 papers, accounting for 4.938%), with the top three sources accounting for 17.695% of the total papers. Bradford's laws were also used for analysis, and the related sources were divided into core, related, and nonrelated areas. The core sources included *Amyotrophic Lateral Sclerosis & Frontotemporal Deg*, *The Cochrane Database of Systematic Reviews*, *Muscle & Nerve*, *Amyotrophic Lateral Sclerosis and other Motor Neuron Disorders*, *Journal of the Neurological Sciences*, *The Lancet*, and *Journal of Neurology*, with 75 articles published by these 7 sources, accounting for 30.864%. It can be seen that there are many relevant sources in this field, and the results are relatively concentrated. Nevertheless, there are still some small groups running independently, which can cooperate with other journals. Therefore, there is still a lot of room for future development for them.

Authors

Bibliometric analysis was carried out on the authors of the references (Fig. 9), and a total of 10 high-frequency authors were obtained. Cudkowicz ME, who published 14 papers, accounting for 5.76%, ranked first; while the author with the second most publications was Shefner JM, who published 11 articles, accounting for 4.53%; and the remaining high-frequency authors published 7–8 articles. In terms of the number of papers published by the authors, the former two constitute the main body of papers and are the core authors, while the total number of papers published by high-frequency authors accounts for 35.39%. This shows that the mainstream author group is relatively fixed, and there should be more communication and cooperation between high-frequency authors. At the same time, the production of the authors over time was studied, and it was found that Miller RG was the earliest high-frequency author to publish articles; he began to study ALS in 1996, which provided valuable experience for the later researchers.

Keywords

The keywords involved in the 243 references were statistically analyzed, and the results are shown in Figure 10. It can be seen that besides human, the most commonly mentioned words in the articles were related to gender and age, which are closely related to the pathogenic characteristics of ALS. Researchers have tried to explore the characteristics of ALS further from these two aspects and have explored its pathogenesis.

By studying the topic trend, we found that the research boom of gender and age appeared from 2012 to 2014. In recent years, the research focus has been on edaravone/therapeutic use as well as ALS/diagnosis/drug therapy. Additional topics include the methods used in clinical trials, including cohort studies, double-blind method, and so on (Fig. 11).

Discussion

The first report on ALS was published in *The Lancet* in the 19th century. Since then, the global incidence of ALS has been increasing; 23.4% of cases were still alive at 5 years and 11.8% at 10 years from the date of diagnosis.[15] Failure of respiratory muscles is the common cause of patients' death.[16] Although scientific and technological advances have led to a new level of motivation and clinical research for ALS, the root causes remain elusive. Bibliometrix is a new bibliometrics analysis software written in R language.[17] It provides a broader perspective for the research process by analyzing countries, institutions, sources, and authors, thus allowing us to have a deeper understanding of development trends.[18]

We found that a total of 32 countries contributed to ALS re-

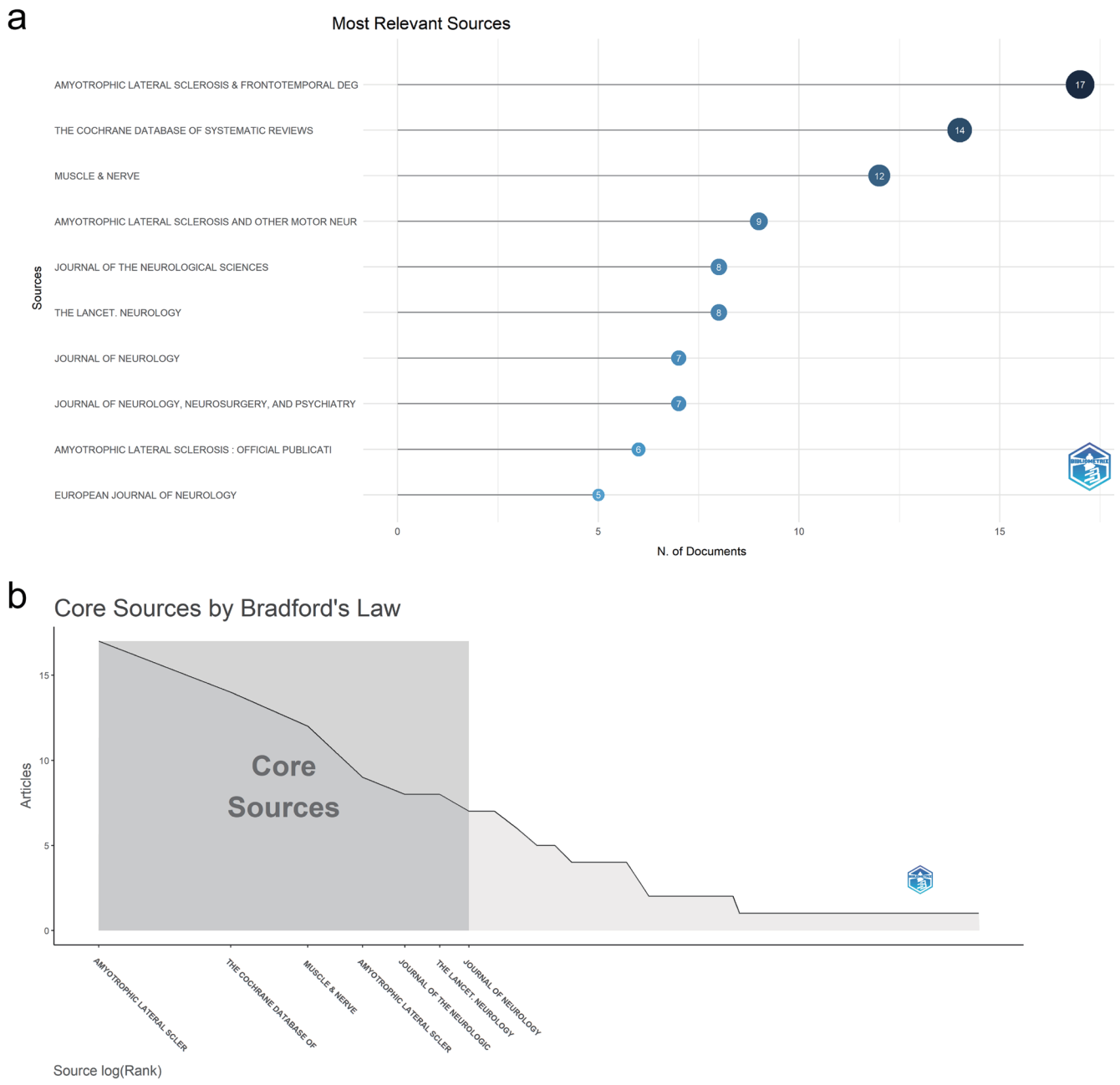

Fig. 8. Most relevant sources (a) and core sources by Bradford's Law (b) of amyotrophic lateral sclerosis studies.

search. The number of papers published by the top five countries was more than 100, among which Italy surpassed the USA as the first.[19] In addition to Japan, South Korea, and China in the top ten, other Asian countries had little research output. It is well known that clinical studies need abundant and sustainable funding.[20] Therefore, a country's production is closely linked with its degree of development. High input usually brings fruitful achievements.

In this study, the literature on ALS treatment from 1991 to 2022 was measured and analyzed. The Biblioshiny scientific research visualization software provides an overview of the basic research on ALS treatment worldwide. The annual production of sources, countries, and institutions were analyzed. Our results revealed that the number of documents is on the rise on the whole. The range of sources has gradually increased, while the country and affiliation have had explosive growth in the past two years. This shows that one of the main reasons for the increase is that countries and institutions have strengthened their cooperation as well as exchanged results while conforming to the scientific research environment.

At the same time, we discovered that similar to other fields, the development degree of ALS is still dominated by Western countries in Figure 12.[20] Because most journals are published in English, English-speaking countries such as the USA have a natural advantage. Nevertheless, this has also led to the phenomenon that some articles from non-English speaking countries have low

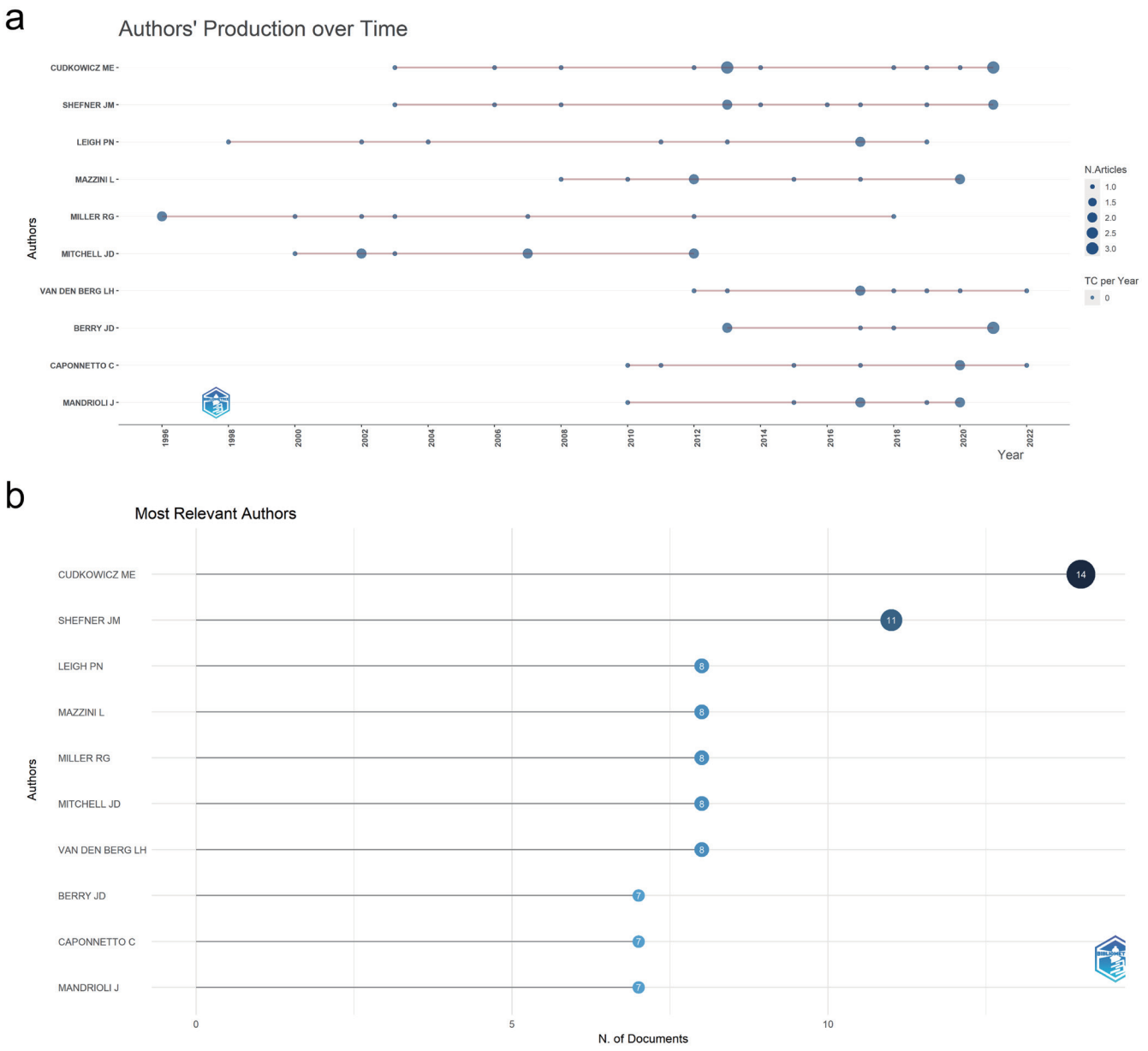

Fig. 9. Authors' production over time (a) and most relevant authors (b) of amyotrophic lateral sclerosis studies.

Fig. 10. Tree maps of amyotrophic lateral sclerosis studies.

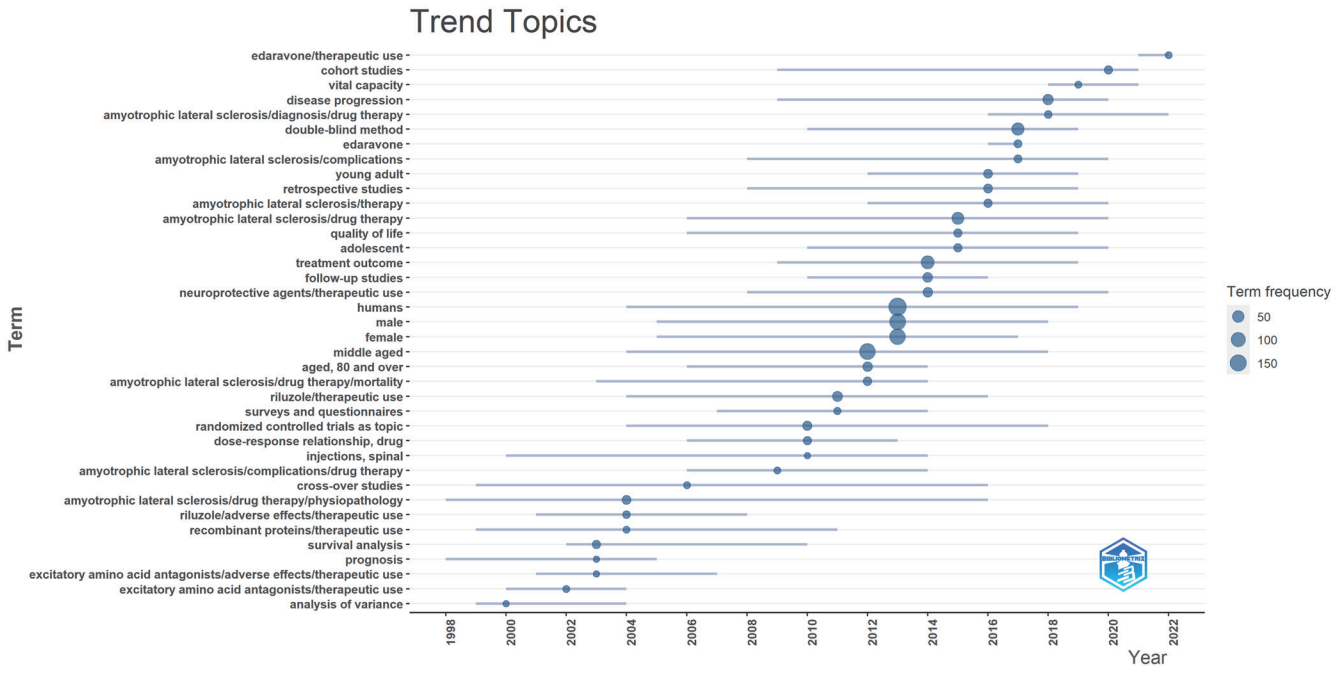

Fig. 11. Trend topics of amyotrophic lateral sclerosis studies.

international acceptance, and the research of authors from certain countries can only be limited to their own country.[21] Therefore, we might have consequently underestimated the contribution of non-English-speaking countries.[22]

Utilizing the software Biblioshiny, the Trend Topics function was used to reveal trends in abstract words.[23] The current research hotspots can be basically divided into four groups: gender, age, treatment, and research methods. In the future, clinical and theoretical research will rise around these aspects and build a more perfect treatment and prevention system.[24] The global incidence of ALS is constantly increasing, but the clinical cure rate is not ideal. However, with the progress of scientific research and technology, there are many emerging technologies compared with the previous ones. With the deeper exploration of the pathogenesis of ALS, we can discover some new targets or related genes as well as develop new therapies according to these mechanisms. In 2022, several new drugs were developed, including tofersen, an antisense oligonucleotide targeting the *SOD1* gene,[25] and AMX0035, with protection of the endoplasmic reticulum and mitochondria.[26] A new treatment that combines stem cells and genetic engineering was also discovered.[27] At the same time as drug development, some new technologies are also moving forward. For example, aiming to alleviate patients' pain due to the atrophy of body muscles in the later stage of disease and allowing the patient to communicate with the outside world, the corresponding technologies were invented: brain-computer interface technology can directly extract the patient's brain waves; and an eye control instrument can be used to spell the content by the time the patient's eye lingers on the character.[28] However, due to the existence of individual differences, before we are ready to use these emerging therapies, we should carefully examine and distinguish which content is sensationalism and which is genuine.

Our study has some limitations that must be addressed. First, the PubMed database offers broader coverage but less rigorous screening processes.[29–31] Therefore, our results may be somewhat general. Second, there is some systematic bias in the length-time effect: Earlier published articles will receive more citations,[32] and earlier topics will occupy a larger proportion. Third, numerous cited references were missed, which makes it impossible to analyze the authority of institutions, sources, or authors.

Conclusion

The output of ALS research has increased steadily over the years, and the USA and Western Europe have contributed significantly to this field.[33] The most relevant source on ALS is that by *Amyotrophic Lateral Sclerosis & Frontotemporal Degeneration*, the most fruitful affiliation is Harvard Medical School, and the most productive and influential author is Cudkowicz ME.

If we can increase cooperation and exchange with scholars or institutions in other countries and conduct research together, it is reasonable to speculate that more meaningful research results will be obtained and that further development in this field will be promoted.

Along with the upgrade of research, cooperative learning is bound to be essential for determining the mechanism of ALS pathogenesis as well as clinical investigations to treat ALS. With datasets and cutting-edge methodology growing, an array of novel ALS-associated genes and mechanisms will be discovered. Consequently, regular reviews should be compiled each year.[34]

Acknowledgments

None to declare.

Funding

This work was supported by the 2022 Research and Cultivation Fund of Capital Medical University—An exploration of the "enteric-muscle" axis mechanism of acupuncture intervention in amyotrophic lateral sclerosis (PYZ22034).

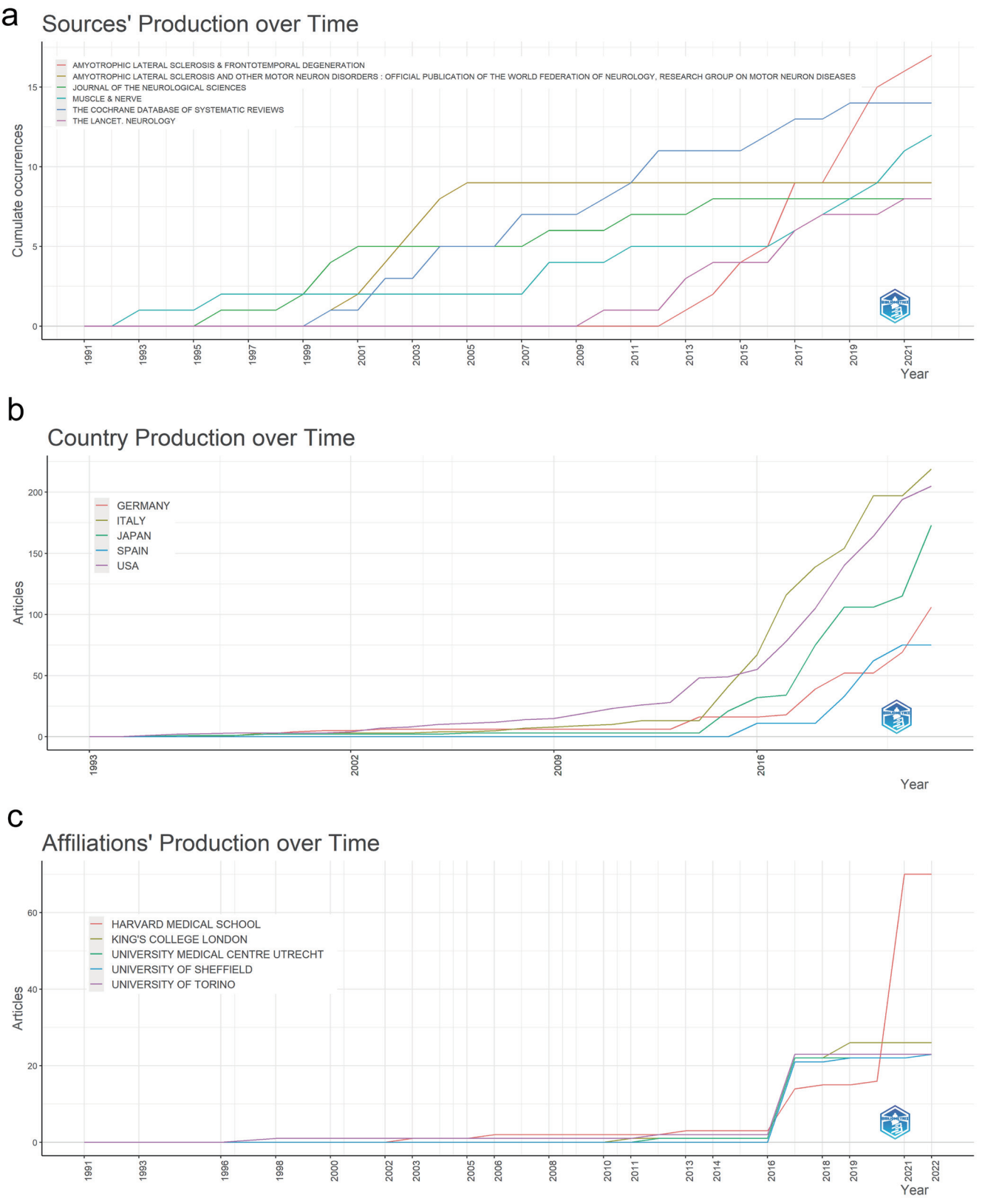

Fig. 12. Sources' production over time (a), country production over time (b), and affiliations' production over time (c) of amyotrophic lateral sclerosis studies.

Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Manuscript drafting (XDY) and supervising (TQW).

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