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Research article

Knowledge mapping of disease-modifying therapy (DMT) in multiple sclerosis (MS): A bibliometrics analysis

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ABSTRACT

Background: Multiple sclerosis (MS) is a heterogeneous autoimmune disease, with a rapidly evolving body of literature on disease-modifying therapy (DMT) that urgently needs to be synthesized and regularized.

Methods: The original material used for the analysis was obtained from the Web of Science Core Collection (WoSCC) in the Science Citation Index Expanded Edition (SCI-E). The data material was accessed through VOSviewer, Citespace, R package "Bibliometrix", and Scimago Graphica for data analysis and visualization. Among them, the clustering algorithm based on the Largest Likelihood Ratio (LLR) and the burst citation algorithm is the key.

Results: As of November 6th, 2022, 4142 publications related to emerging disease-modifying therapies (e-DMT) for MS, 6521 publications related to traditional disease-modifying therapies (t-DMT) for MS, and 1793 publications in cross-cutting disease-modifying therapies (I-DMT) for MS were included in the analysis, respectively. Publications related to DMT in MS were analyzed descriptively (for three subjects: country, institution, and author) and predictively (for two subjects: keywords and references) separately according to three sections: e-DMT, t-DMT, and I-DMT. Topics that still have relevant reference output as of 2022 include the safety of Coronavirus disease 2019 (COVID-19) mRNA vaccination, therapeutic inertia (TI), cladribine tablets, autologous hematopoietic stem cell transplantation (aHSCT), progressive multiple sclerosis, and pediatric multiple sclerosis.

Conclusion: The future research focus for MS DMT is the combination trial or cross-trial of various treatment methods to improve the development of individualized treatment plans for MS patients. The exact contents of the research frontiers are included but not limited to ocrelizumab, fingolimod and other monoclonal antibodies, fumaric acid ester, cladribine tablet, aHSCT, and other interventions of randomized controlled trials (RCTs); the impact of mRNA COVID-19 vaccination on MS patients; TI, patient adherence, and other medical management issues; and continued exploration of biomarkers for more accurate disease classification based on the existing clinical indication classification.

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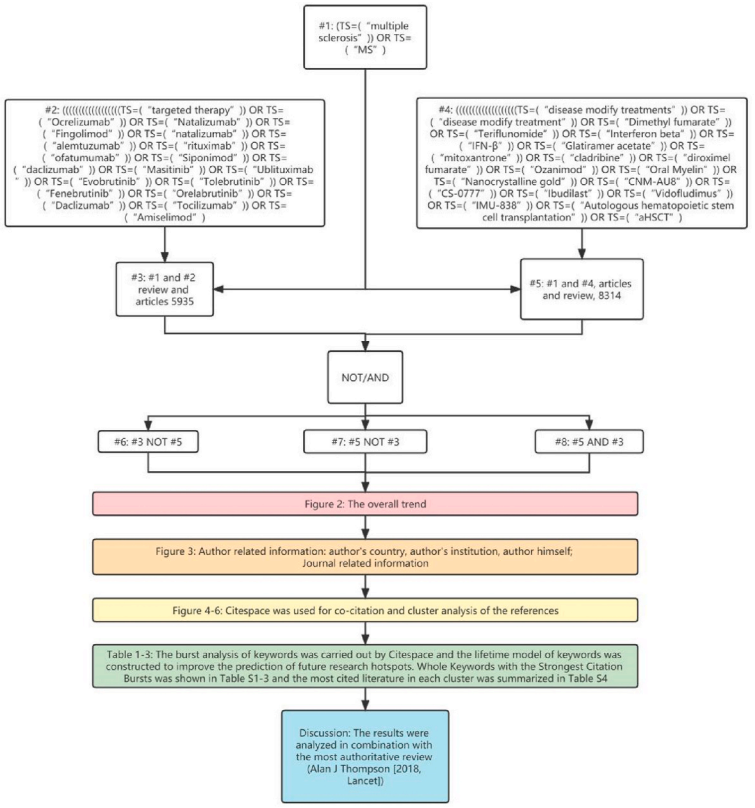
A



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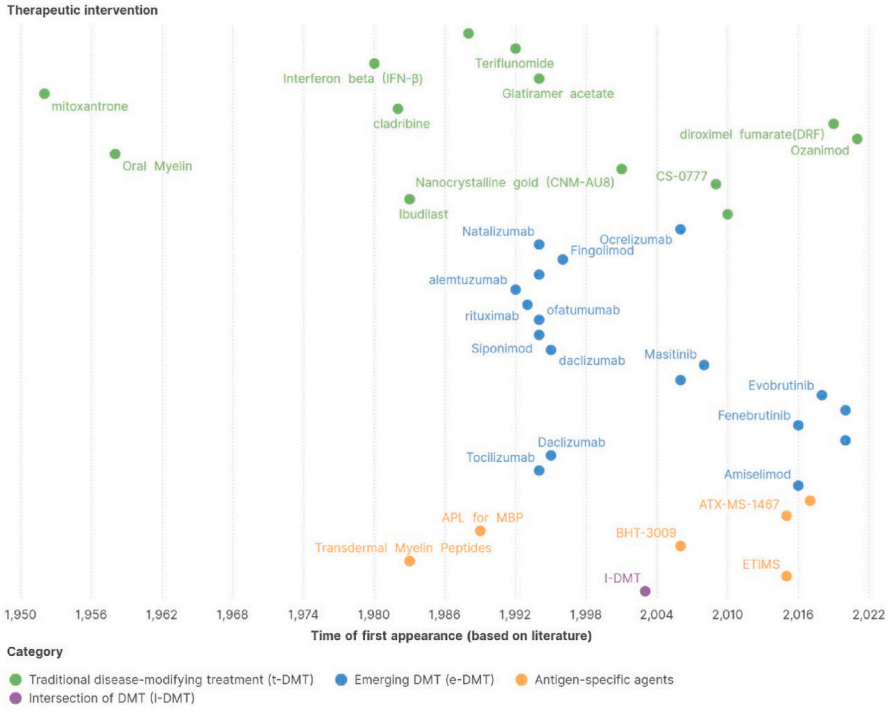

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Fig. 1. Schematic representation of the literature search formula and the time of the first appearance of keywords. (A) Retrieval strategy and logical thought. #1 indicates retrieval of MS-related content. #2 denotes the retrieval of e-DMT-related content with "targeted therapy, Ocrelizumab, Natalizumab, Fingolimod, natalizumab, alemtuzumab, rituximab, ofatumumab, Siponimod, daclizumab, Masitinib, Ublituximab, Evobrutinib, Tolebrutinib, Fenebrutinib, Orelabrutinib, Daclizumab, Tocilizumab, Amiselimod " as keywords for the search. #3 Indicates retrieval of MS e-DMT related literature. #4 Indicates retrieval of t-DMT related content with the keywords "diseases modify treatment(s), Dimethyl fumarate (DMF), Teriflunomide, Interferon beta (IFN-β), Glatiramer acetate, mitoxantrone, cladribine, diroximel fumarate(DRF), Ozanimod, Oral Myelin, Nanocrystalline gold (CNM-AU8), CS-0777, Ibudilast, Vidofludimus (CNM-AU8), Ibudilast (CNM-AU8), Ibudilast (CNM-AU8), Ibudilast (CNM-AU8) Vidofludimus (IMU-838)" were searched. #5 indicates the acquisition of MS t-DMT-related literature. #6 indicates that the acquired MS e-DMT-related literature needs to be removed from containing MS t-DMT-related literature to be the true e-DMT-related literature for our target analysis. #7 denotes that the MS t-DMT-related literature obtained needs to be removed from the MS e-DMT-related literature to be the true t-DMT-related literature that we aim to analyze. #8 Indicates that the MS t-DMT-related literature acquired needs to be combined with the MS e-DMT-related literature to be the true I-DMT-related literature for our target analysis. The pink color block indicates that we first describe the overall characteristics of e-DMT, t-DMT, and I-DMT in Fig. 2. The orange color block indicates that we will analyze author-related information in Fig. 3. The yellow color block indicates that we will show the results of co-citation and cluster analysis of references based on CiteSpace for visual presentation in Figs. 4–6. The contents of the green color block and cyan color block have been explained in detail in Fig. (B) To make it easier for the reader to understand and get an immediate sense of when the various interventions first appeared, we searched PubMed for the keywords used in the search formula and visualized when the keywords first appeared. Detailed information and reference information we place in Table S5.

1. Introduction

Multiple sclerosis (MS) is a disease of the central nervous system characterized by inflammatory demyelination [1]. The pathology of MS includes inflammatory and neurodegenerative mechanisms affecting white and grey matter [2]. Typically, MS occurs in young adults and women, and as relapse striking accumulates, MS patients' pathological lesions also accumulate [3]. Therefore, there is an urgent need to develop effective treatments. Among current treatments for MS, disease-modifying therapies (DMT), is a type of treatment that can reduce the risk of relapses and decrease disease activity [4]. Then the course of MS can be changed, and the accumulation of MS symptoms can be slowed down. Research on etiology, susceptibility genes, and DMT has been successful [5].

However, with many researchers focusing on DMTs, more than 100,000 academic papers associated with MS can be searched on the Web of Science, but reading all this literature is an impossible mission [6]. At the same time, in the current post-epidemic era, the time and energy of medical professionals appear to be even more precious. Therefore, how to establish a basic understanding of the target subject area quickly and effectively for researchers: e.g., which countries, institutions, and authors have made outstanding contributions to MS research? which references are widely followed by MS researchers? and which keywords are current or even future hot topics? A highly generalized report with guidance is urgently needed [7].

Bibliometrics can analyze the study of academic publishing, and use statistics to describe journals and publication trends, eventually to find relationships between publications in specific research [8]. Thus, we adopt a bibliometric approach to study and analyze MS DMTs into three elements and six levels. The three elements are emerging DMT (e-DMT), traditional DMT (t-DMT), and the intersection of e-DMT and t-DMT (hereafter referred to as the intersection of DMT (I-DMT)). Considering the possibility of mixing I-DMT-related articles in e-DMT and t-DMT, we searched e-DMT and t-DMT by excluding all contents in the I-DMT section to ensure the simplicity and reliability of e-DMT and t-DMT as well as the plurality of I-DMT. The six dimensions are country/region, research institution, researcher, journal, reference, and keyword [9]. Through analysis of the three elements and six levels, the new powerful tool of bibliometrics can complete the description of the current status of MS treatment research; at the same time, it can help researchers target the most informative references and keywords of the present, enabling them to identify future research hotspots [10].

2. Materials and methods

2.1. Data materials

The Science Citation Index Expanded (SCI-E) database in the Web of Science Core Collection (WoSCC) was chosen as the source of access to primary materials for the following reasons: 1) SCI-E provides the bibliometric SCI-E provides the file formats required by bibliometric analysis software such as Citespace, VOSviewer, Scimago Graphica, and Bibliometrix; 2) SCI-E database is the most commonly used database for searching articles; and 3) SCI-E includes more authoritative and comprehensive articles than other databases [6,7,9–11].

2.2. Methods

2.2.1. Retrieval strategies and logical framework

We conducted the reference search and collection on November 6, 2022, which took 8 h to ensure that the bias caused by the search time was as slight as possible. The specific search formula was shown in the non-colored box in Fig. 1A. We laid a good bibliometric foundation through the preliminary bibliometric work [6,7,9–11], the discussion of several experts and professors (T.C. and C.Z.), and the analysis of related literature, we finally locked the keywords as shown in Fig. 1. The following principles should be followed in the search: 1) Since original articles and reviews play the most critical role in the dissemination of disciplinary knowledge, only original articles and reviews were included; 2) Since there was significant variability in the classification of treatments in all current articles, for

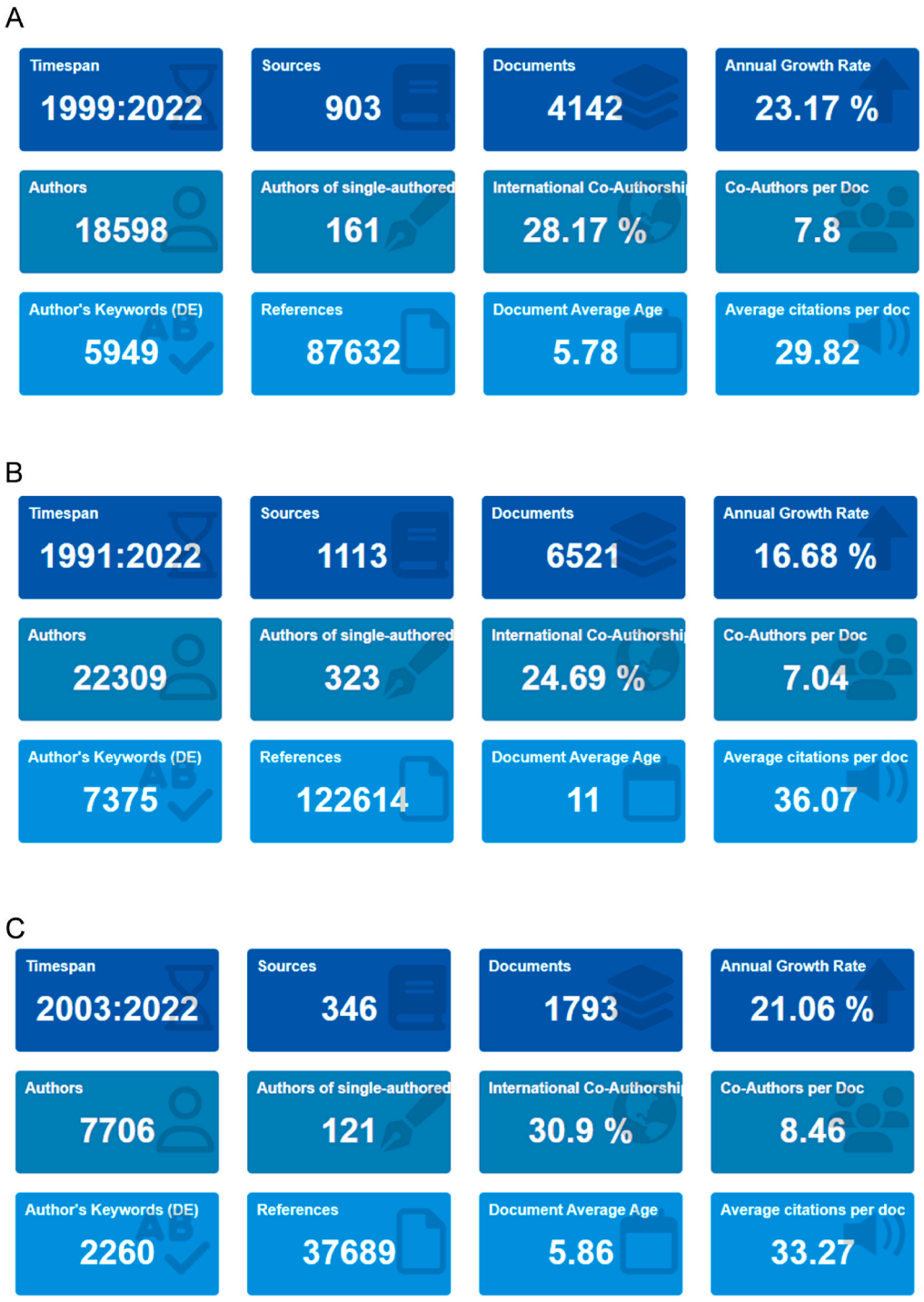

Fig. 2. Evaluate the overall trend of the three factors from twelve indicators. (A) e-DMT; (B) t-DMT; (C) I-DMT. The first content was the time span of these studies. E-DMT began in 1999, t-DMT began in 1991, and I-DMT started in 2003, consistent with clinical practice because t-DMT relieved the patient's symptoms significantly ahead of any other DMTs. Around the 21st century, targeted therapy and other e-MDT have also been added to the treatment of MS with the development of targeted drugs. Their comparison was naturally conducted after basic research on both t-DMT and e-DMT therapy. Since t-DMT-related treatment strategies appeared earliest, they contained the most significant number of journals (1133). Since e-DMT had just been developed in the last 20 years, it included an intermediate number of journal types (903, between 346 and 1133). Since I-DMT grew in the past ten years, I-DMT held the least number of journals (346). The number of published articles for this three-factor was 4,142, 6,521, and 1793. The annual growth rate of published articles was 23.17%, 16.68%, and 21.06%, respectively. The number of authors in this three-factor was 18,598, 22,309, 7706; the number of articles published by a single author was 161, 323, 121. The proportion of international cooperation

publications was 28.17%, 24.69%, and 30.9%, respectively. The average number of authors per article was 7.8, 7.04, and 8.46. The keywords given by the authors were 5,949, 22,309, and 7706. The cited references were 87,632, 122,614, and 37,689. The average life of each article from publication to citation reduction was 5.78, 11, and 5.86. Since most of the references on e-DMT and I-DMT had emerged in the last two decades, the average life expectancy was influenced by the time of publication, and therefore, there would be a mistake in predicting the average life for three-factor. Finally, the average citation times of each article were 29.82, 36.07, and 33.27.

ease of reading and understanding, we divided the treatments of MS into three factors (explained above) for the study. 3) bibliometrics consisted of six basic levels of analysis (for a specific explanation of the six levels, see above, and the analysis steps were shown in the colored boxes in Fig. 1A); 4) most of the current mainstream bibliometric analyses focus only on burst analysis. To make the keyword prediction and analysis more rigorous, we simulated the construction of a keyword lifetime model based on the results of keyword emergence to enhance the rigor of keyword prediction. 5) Electronic databases and computer analysis generated the previous four steps entirely. To improve the relevance of the results and the accuracy of the prophecy, we integrated the analysis of references that still had a high number of citations and keywords with a high frequency of occurrence in 2022 to ensure maximum accuracy in predicting future research hotspots. To make it easier for the reader to understand and get an immediate sense of when the various interventions first appeared, we searched PubMed for the keywords used in the search formula and visualized when the keywords first appeared (Fig. 1B). Detailed information and reference information we place in Table S5.

2.2.2. Data extraction

Microsoft Excel365 (Microsoft, Raymond, Washington, The United States of America (USA)) was used for further processing, and two researchers (F.J. and Y·S.) independently carried out data extraction and reference selection and analysis to ensure the reliability of the results. A third-party consultation (T.C.) would involve reaching a reliable conclusion when a disagreement is still unresolved. The number of publications, the average citation per article, and the H-index were automatically generated by the SCI-E citation report. The H-index, assessing the scientific research influence and productivity of countries/regions/institutions/researchers/journals, is calculated from h papers published by countries/regions/institutions/researchers/journals, each of which is cited at least h times [12,13].

2.2.3. Data visualization and analysis

Software (CiteSpace (6.1. R4), Bibliometrix, and VOSviewer (1.6.18)) produced the knowledge network map, and GraphPad Prism and Microsoft Excel 365 analyzed the data.

2.2.4. CiteSpace

CiteSpace (version 6.1. R4, available for download at https://sourceforge.net/projects/citespace/) is a software developed by Professor Chen based on the Java language, known for its highly influential visualization software loaded with burst analysis and cluster analysis, which allows for obtaining quantitative information and discover specific scientific research fields relevant developments and trends [14].

2.2.5. VOSviewer

VOSviewer (version 1.6.18, The Netherlands, available for free on the download at http://vosviewer.com) is a software tool developed by Ike and Waltman at Leiden University based on a JAVA framework that constructs and visualizes bibliometric networks [15].

2.2.6. Bibliometrix

Bibliometrix (download package Bibliometrix 4.0.1; https://www.bibliometrix.org/home/) is a package created and developed by Massimo Aria and Corrado Cuccurullo for the R statistical programming language (R Studio software 2022.07.2 (R version 4.2.1 (2022-06-23 ucrt)) for quantitative research in scientometrics and bibliometrics [16].

2.3. Statistical analysis

GraphPad Prism 8 (San Diego, CA, USA) and Microsoft Excel 365 (Microsoft Corporation) did the work of statistical analysis.

3. Result

3.1. Acquisition of material for analysis

Based on the three-factor retrieval results, the logical framework of our specific expanded content was presented in the colored box in Fig. 1A. E-DMTs prefer drugs developed on immune principles; t-DMTs prefer chemical synthetics/active metabolites/high-performance material-based drugs [17].

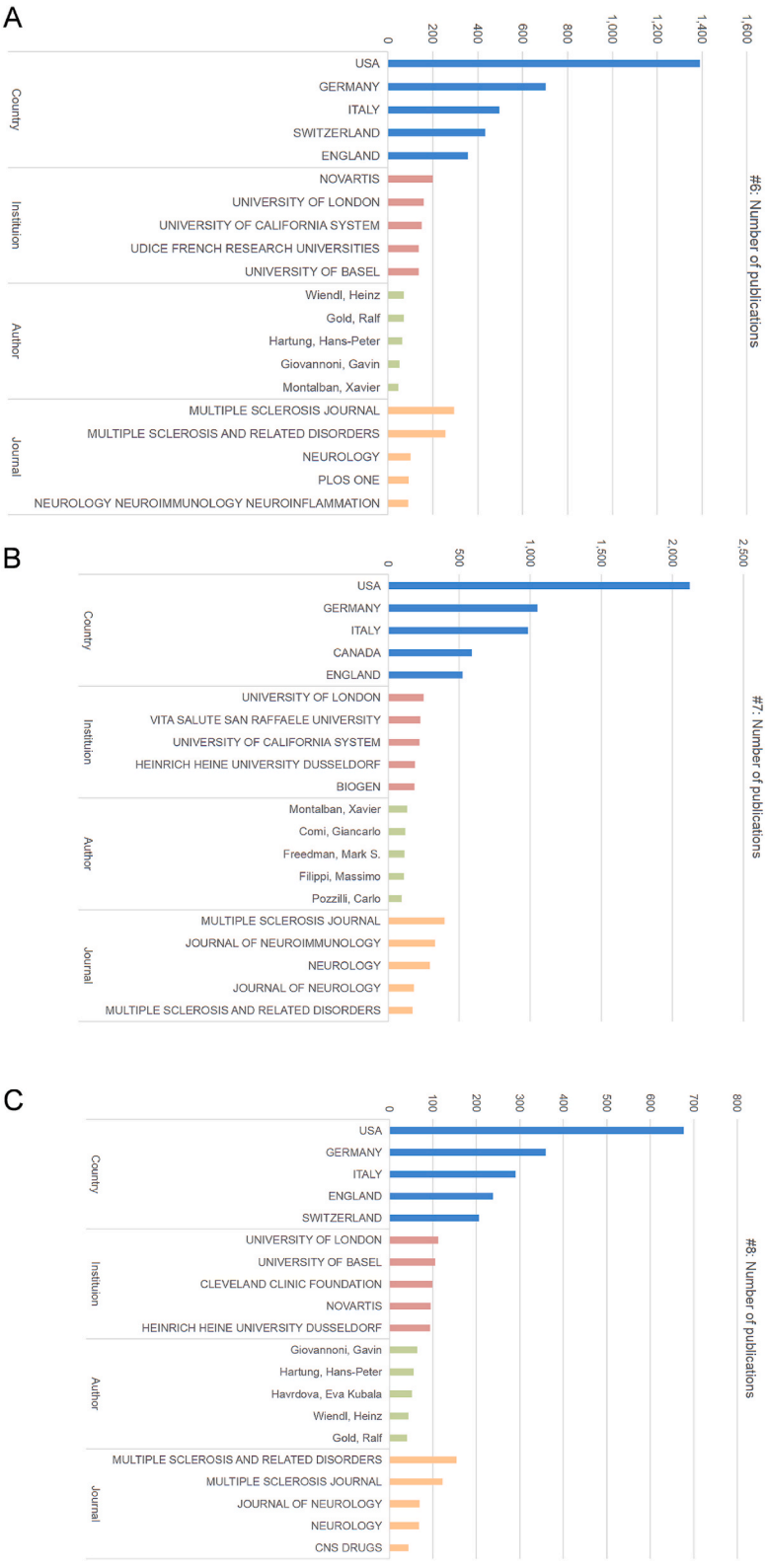

Fig. 3. Evaluation of the performance of the three factors in the number of publications from the four levels of the country, institution, researcher, and journal (A) e-DMT; (B) t-DMT; (C) I-DMT.

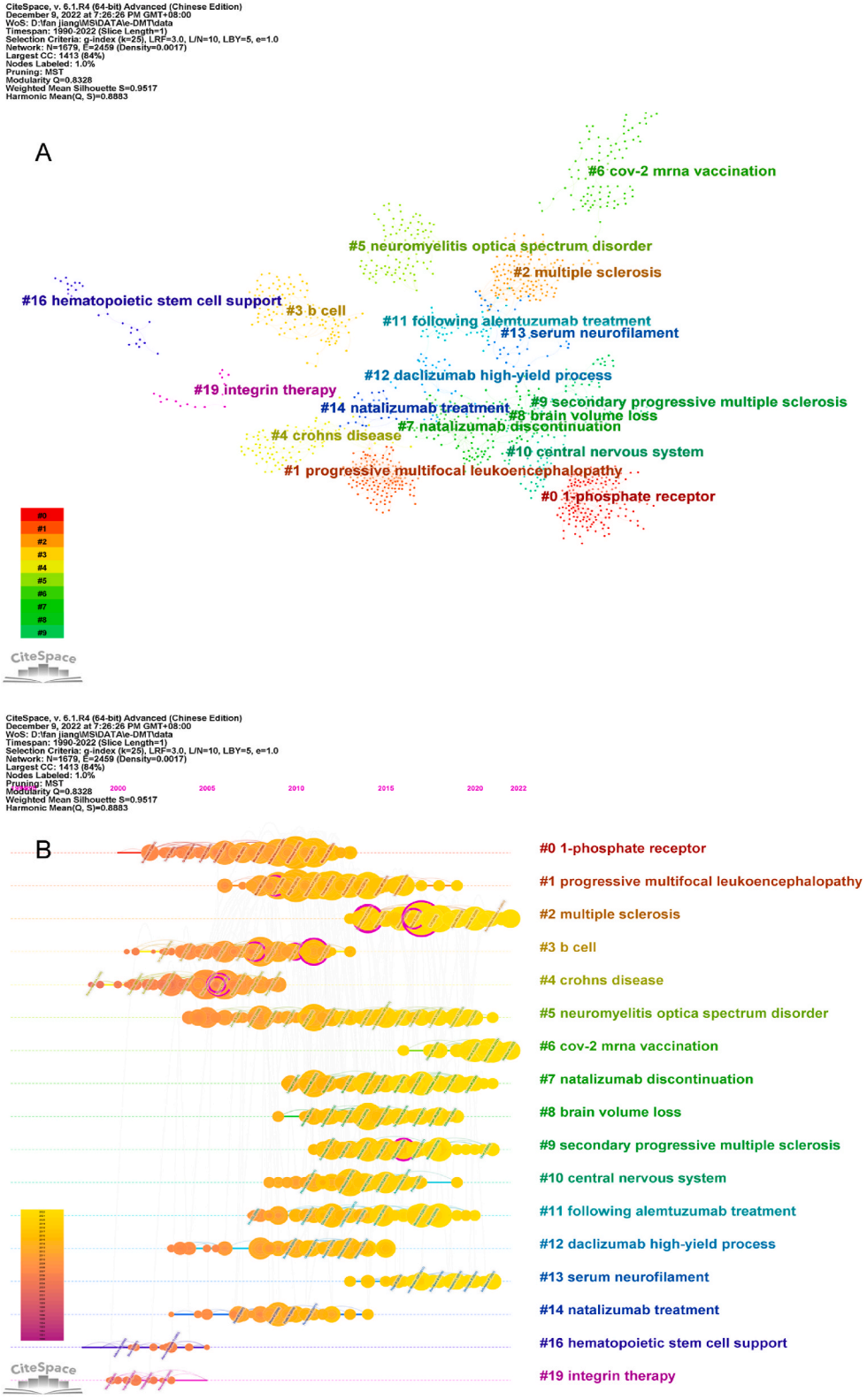

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Fig. 4. Co-citation and cluster analysis of related references of e-DMT based on Citespace (A) Clustering network graph. Sampling and data analysis were performed based on Citespace using the parameters identified in the figure, where a circle indicates a piece of literature and the same color indicates attribution to a cluster, and cluster labels were obtained based on the words in the titles and abstracts of the literature under that cluster using the maximum likelihood ratio method. (B) Clustering timeline map. The purple numerical labels indicate when the literature appeared. A circle in the figure represents a piece of literature, and a circle with purple color indicates that the literature has a high mediational centrality, which can be interpreted as literature that has had a profound impact on the research of MS DMT. The earlier appearance of the circle indicates that the related research subclass of the cluster was developed earlier, and the later appearance of the circle indicates that the related research subclass of the cluster is still in a hot research state in recent years.

3.2. The research status of MS

The first content was the time span of these studies. E-DMT began in 1999, t-DMT began in 1991, and I-DMT started in 2003, consistent with clinical practice because t-DMT relieved the patient's symptoms significantly ahead of any other DMTs (Fig. 2). Around the 21st century, targeted therapy and other e-MDT have also been added to the treatment of MS with the development of targeted drugs. Their comparison was naturally conducted after basic research on both t-DMT and e-DMT therapy. Since t-DMT-related treatment strategies appeared earliest, they contained the most significant number of journals (1133). Since e-DMT had just been developed in the last 20 years, it included an intermediate number of journal types (903, between 346 and 1133). Since I-DMT grew in the past ten years, I-DMT held the least number of journals (346). The number of published articles for this three-factor was 4,142, 6,521, and 1793. The annual growth rate of published articles was 23.17%, 16.68%, and 21.06%, respectively. The number of authors in this three-factor was 18,598, 22,309, 7706; the number of articles published by a single author was 161, 323, 121. The proportion of international cooperation publications was 28.17%, 24.69%, and 30.9%, respectively. The average number of authors per article was 7.8, 7.04, and 8.46. The keywords given by the authors were 5,949, 22,309, and 7706. The cited references were 87,632, 122,614, and 37,689. The average life of each article from publication to citation reduction was 5.78, 11, and 5.86. Since most of the references on e-DMT and I-DMT had emerged in the last two decades, the average life expectancy was influenced by the time of publication, and therefore, there would be a mistake in predicting the average life for three-factor. Finally, the average citation times of each article were 29.82, 36.07, and 33.27 (Fig. 2).

3.3. Top five countries, institutions, researchers, and journals in MS

In the field of e-DMT for MS (Fig. 3A), countries ranked top 5 globally in the number of publications were the USA(1390) > Germany(703) > Italy(496) > Switzerland(433) > England(356); institutions were Novartis(199) > University of London(160) > University of California(150) > Udice, French research universities(137) > University of Basel(137); researchers were: Wiendl Heinz(71) > Gold Ralf(70) > Hartung Hans-Peter(65) > Giovannoni Gavin(50) > Montalban Xavier(47); journals were: Multiple Sclerosis Journal (294) > Multiple Sclerosis and Related Disorders(256) > Neurology(101) > PLOS ONE(91) > Neurology Neuroi*mmunology & Neuroinflammation*(89).

In the field of t-DMT for MS (Fig. 3B), countries ranked top 5 globally were: the USA(2,121) > Germany(1,050) > Italy(984) > Canada(590) > England(524); institutions were: University of London(248) > Vita-Salute San Raffaele University(225) > University of California(219) > Heinrich Heine University Düsseldorf(137) > Biogen(137); researchers were: Montalban Xavier(133) > Comi Giancarlo(119) > Freedman Mark S.(114) > Filippi Massimo(110) > Pozzilli Carlo(96); journals were: Multiple Sclerosis Journal(397) > Journal of Neuroimmunology(329) > Neurology(292) > Journal of Neurology(182) > Multiple *Sclerosis and Related Disorders*(172).

In the field of IA-MDT for MS (Fig. 3C), countries ranked top 5 globally were: USA(677) > Germany(360) > Italy(290) > England (239) > Switzerland(206); institutions were: University of London(112) > University of Basel(105) > Cleveland Clinic Foundation(99) > Novartis(95) > Heinrich Heine University Düsseldorf(94); researchers were: Giovannoni Gavin(64) > Hartung Hans-Peter(56) > Havrdova Eva Kubala(52) > Wiendl Heinz(44) > Gold Ralf (41); journals were: Multiple Sclerosis and Related Disorders(154) > Multiple Sclerosis Journal(123) > Journal of Neurology(69) > Neurology(68) > CNS Drugs(44).

3.4. Co-citation and cluster analysis of references

Reference related to e-DMT of MS was divided into 17 parts through co-citation and cluster analysis (Fig. 4): #0 "1-phosphate receptor"; #1 "progressive multifocal leukoencephalopathy"; #2 "multiple sclerosis"; #3 "b cell"; #4 "crohns disease"; #5 "neuromyelitis optica spectrum disorder"; #6 "cov-2 mRNA vaccination"; #7 "natalizumab discontinuation"; #8 "brain volume loss"; #9 "secondary progressive multiple sclerosis"; #10 "central nervous system"; #11 "following alemtuzumab treatment"; #12 "daclizumab high-yield process"; #13 "serum neurofilament"; #14 "natalizumab treatment"; #16 "hematopoietic stem cell support"; #19 "integrin therapy."

References related to t-DMT for MS were divided into 19 parts through co-citation and cluster analysis (Fig. 5): #0 "matrix metalloproteinases"; #1 "interferon beta-1b"; #2 "therapeutic inertia"; #3 "spinal cord atrophy"; #4 "fumaric acid ester"; #5 "glatiramer acetate"; #6 "disease-modifying treatment"; #7 "neutralizing antibodies"; #8 "mitoxantrone treatment"; #9 "gamma-induced class-ii major histocompatibility complex gene-transcription"; #10 "interferon beta therapy"; #11 "regulatory effect"; #12 "long-term result"; #13 "cladribine tablet"; #14 "autologous hematopoietic stem cell transplantation"; #15 "patient adherence"; #16 "neuromyelitis optica"; #17 "randomized controlled trial"; #18 "several clinical"; #19 "health-related quality."

References related to I-DMT for MS were divided into 19 parts through co-citation and cluster analysis (Fig. 6): #0 "comparative

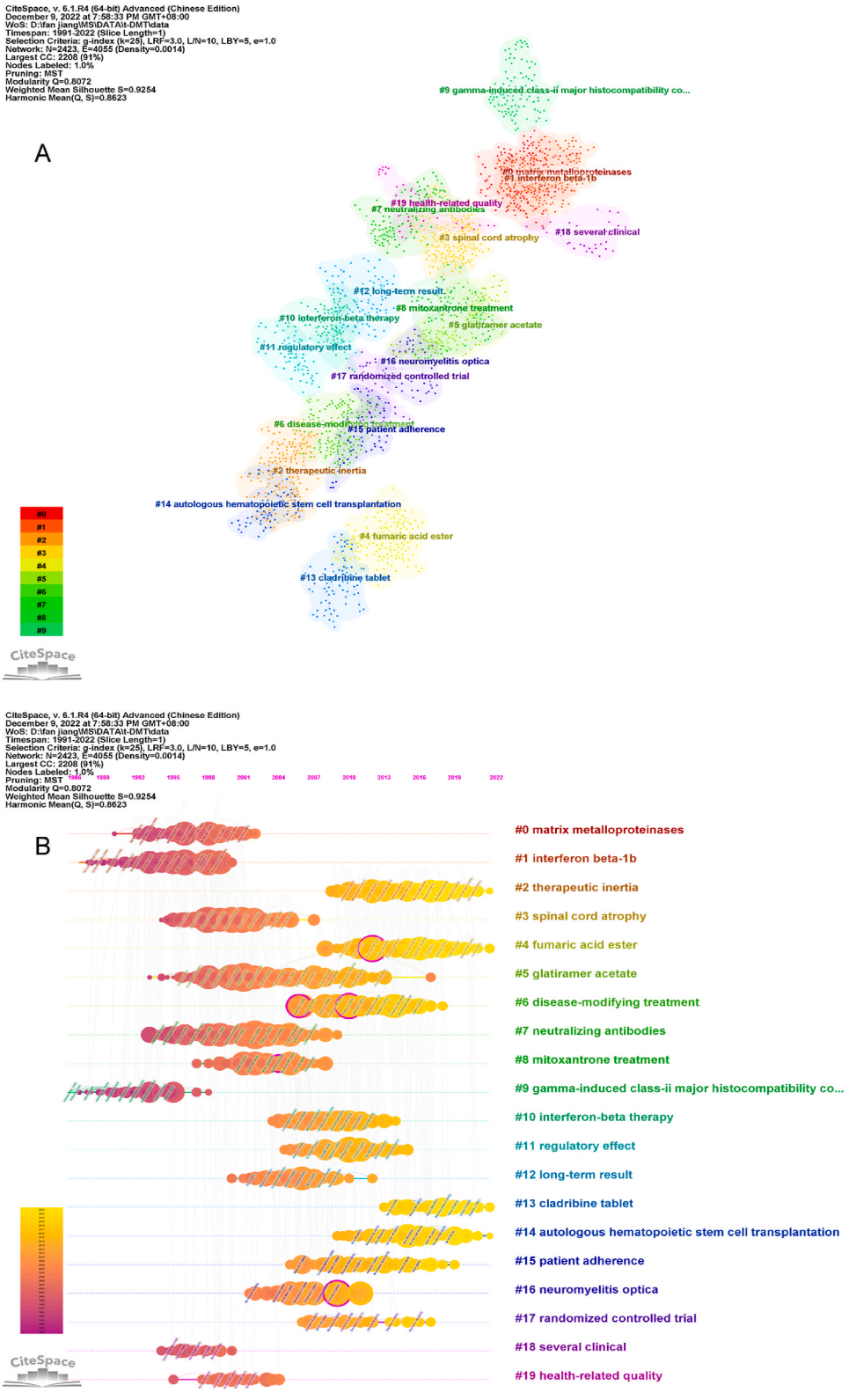


Fig. 5. Co-citation and cluster analysis of related references of t-DMT based on Citespace.

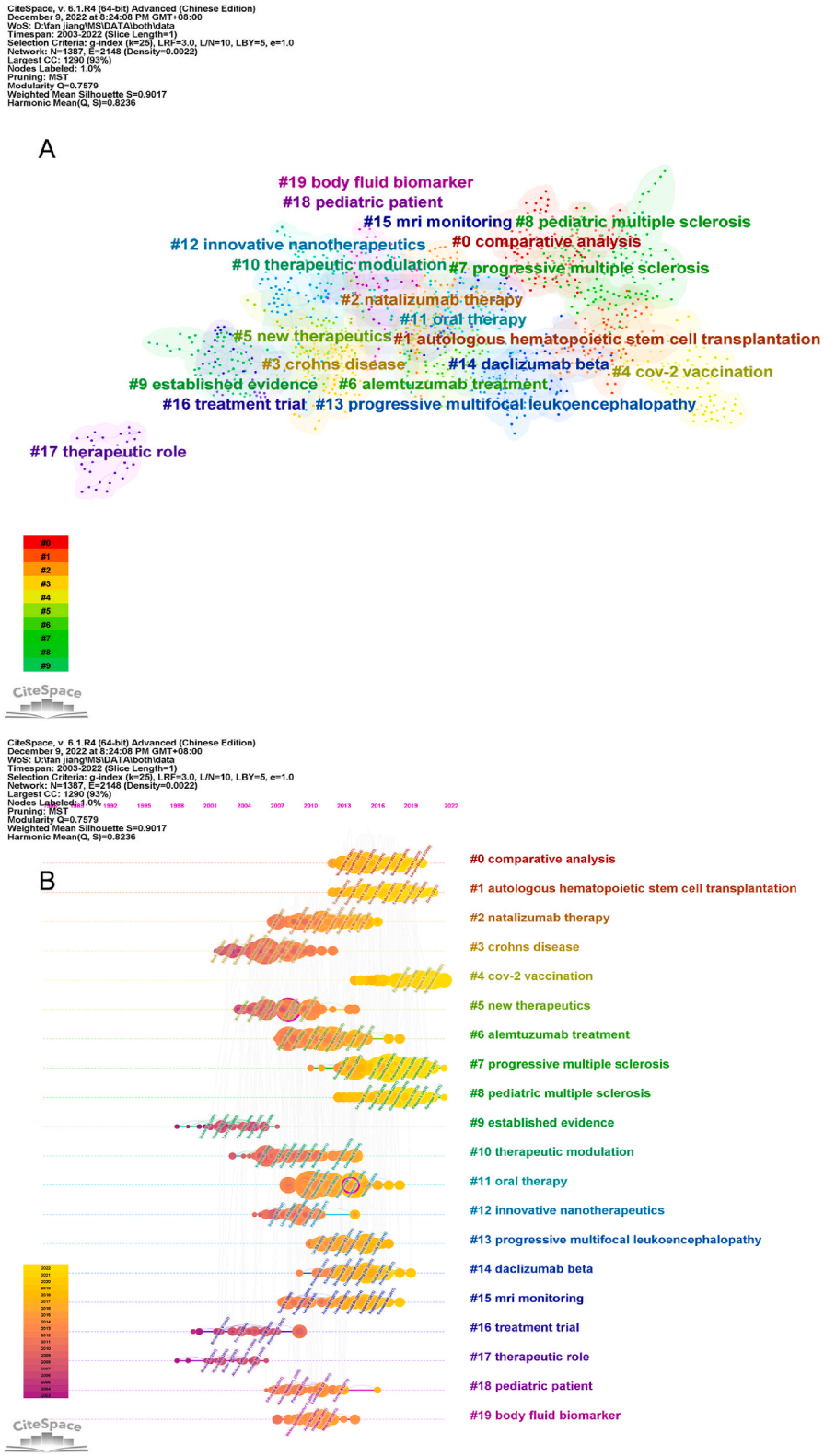
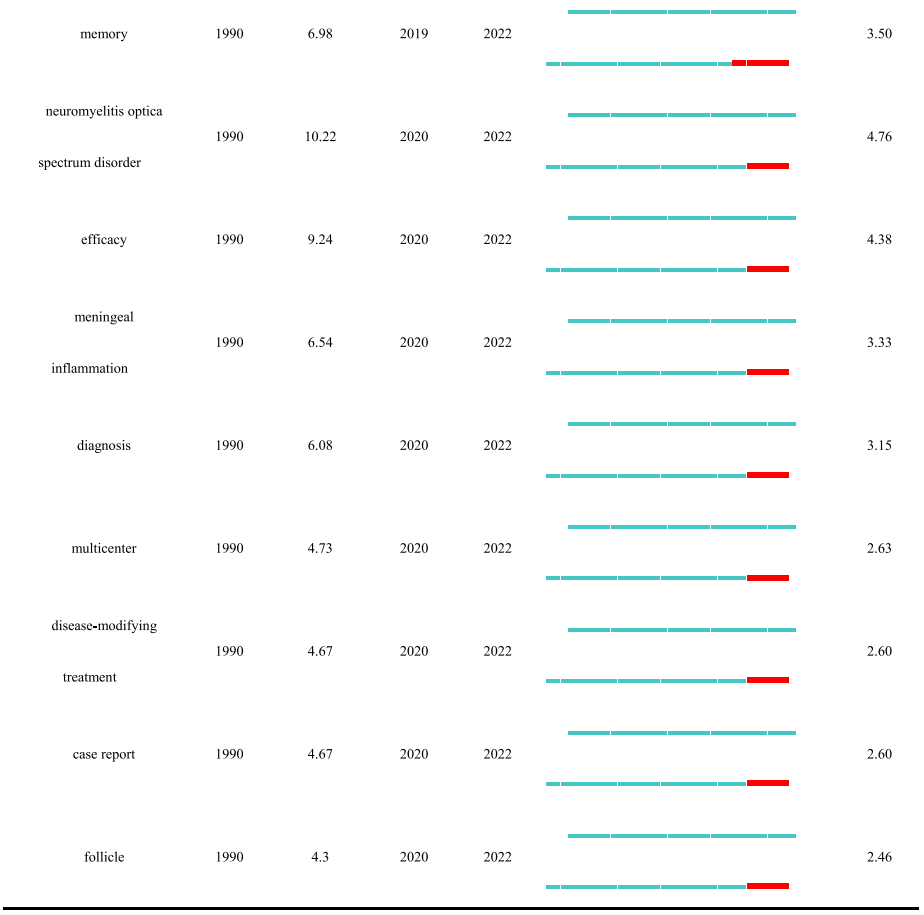


Fig. 6. Co-citation and cluster analysis of related references of I-DMT based on Citespace.

Table 1
(#6)Keywords still in burst citation status in 2022. The blue line indicates the baseline state, and the red line indicates the period when the burst citation intensity is the highest.

Keywords	Year	Strength	Begin	End	1990 - 2022	Predicted lifetime(year)
brain atrophy	1990	7.33	2017	2022		3.64
mouse model	1990	5.15	2017	2022		2.79
impact	1990	5.13	2017	2022		2.78
binding	1990	4.43	2017	2022		2.51
ocrelizumab	1990	28.35	2018	2022		11.81
outcome	1990	7.35	2018	2022		3.65
women	1990	7.05	2018	2022		3.53
disease modifying therapy	1990	6.54	2018	2022		3.33
reconstitution	1990	5.29	2018	2022		2.85
autoimmunity	1990	4.68	2018	2022		2.61
placebo	1990	20.78	2019	2022		8.87
safety	1990	12.4	2019	2022		5.61
oxidative stress	1990	7.77	2019	2022		3.81



analysis"; #1 "autologous hematopoietic stem cell transplantation"; #2 "natalizumab therapy"; #3 "crohns disease"; #4 "cov-2 vaccination"; #5 "new therapeutics"; #6 "alemtuzumab treatment"; #7 "progressive multiple sclerosis"; #8 "pediatric multiple sclerosis"; #9 "established evidence"; #10 "therapeutic modulation"; #11 "oral therapy"; #12 "innovative nanotherapeutics"; #13 "progressive multifocal leukoencephalopathy"; #14 "daclizumab beta"; #15 "mri monitoring"; #16 "treatment trial"; #17 "therapeutic role"; #18 "pediatric patient"; #19 "body fluid biomarker".

3.5. Burst analysis and lifetime model construction of keywords related to MS treatment

All keywords associated with e-DMT for MS that were still in burst citation were shown in Table S1. Keywords still in burst citation status in 2022 were presented in Table 1, including "brain atrophy," "mouse model," "impact," "binding," "ocrelizumab," "outcome," "women," "disease-modifying therapy," "reconstitution," "autoimmunity," "placebo," "safety," "oxidative stress," "memory," "neuromyelitis optica spectrum disorder" (ps: neuromyelitis optica has historically been confused with MS, hence neuromyelitis optica was also detected by the algorithm), "efficacy," "meningeal inflammation," "diagnosis," "multicenter," "disease-modifying treatment," "case report," "follicle."

All keywords associated with the t-DMT for MS were shown in Table S2. Keywords that were still in burst citation status in 2022 were shown in Table 2, including "disease-modifying therapy," "placebo-controlled phase 3", "oral bg 12", "oral teriflunomide," "nf kappa b," "drug," "disability progression," "dimethyl fumarate," "oxidative stress," "risk," "association," "outcome," "activation," "relapsing multiple sclerosis," "relapsing-remitting multiple sclerosis," "inflammation," "adherence," "safety," "pathway," "treatment response," "oral cladribine," "response," "placebo," "cladribine tablet," "persistence," "biomarker," "nrf2", "pharmacokinetics."

All keywords associated with I-DMT with citation burst characteristics were listed in Table S3. The keywords that remained in the burst citation status in 2022 were shown in Table 3, including "relapse," "ocrelizumab," "fingolimod," "placebo," "outcome," "childhood," "children," "oral cladribine," "stem cell transplantation," "alemtuzumab," "predictor," "disease-modifying therapy," "network meta-analysis," "adverse event."

Table 2
(#7)Keywords still in burst citation status in 2022. The blue line indicates the baseline state, and the red line indicates the period when the burst citation intensity is the highest.

Keywords	Year	Strength	Begin	End	1990 - 2022	Predicted lifetime(year)
disease-modifying therapy	1991	24.84	**2014**	2022		5.00
placebo controlled phase 3	1991	54.58	**2015**	2022		5.00
oral bg 12	1991	38.71	**2015**	2022		5.00
oral teriflunomide	1991	24.64	**2015**	2022		5.00
nf kappa b	1991	16.85	**2015**	2022		5.00
drug	1991	11.27	**2015**	2022		5.00
disability progression	1991	7.42	**2015**	2022		3.00
dimethyl fumarate	1991	81.55	**2016**	2022		5.00
oxidative stress	1991	30.39	**2016**	2022		5.00
risk	1991	17.62	**2016**	2022		5.00
association	1991	12.25	**2016**	2022		5.00
outcome	1991	11.87	**2016**	2022		5.00
activation	1991	15.81	**2017**	2022		5.00

relapsing multiple sclerosis	1991	11.35	**2017**	2022	5.00
relapsing-remitting multiple sclerosis	1991	10.4	**2017**	2022	5.00
inflammation	1991	9.88	**2017**	2022	5.00
adherence	1991	8.54	**2017**	2022	5.00
safety	1991	19.86	**2018**	2022	5.00
pathway	1991	8.49	**2018**	2022	5.00
treatment response	1991	7.82	**2018**	2022	4.00
oral cladribine	1991	14.23	**2019**	2022	5.00
response	1991	6.77	**2019**	2022	3.00
placebo	1991	6.47	**2019**	2022	3.00
cladribine tablet	1991	9.17	**2020**	2022	5.00
persistence	1991	8.14	**2020**	2022	5.00
biomarker	1991	7.94	**2020**	2022	5.00
nrf2	1991	7.56	**2020**	2022	4.00
pharmacokinetics	1991	5.95	**2020**	2022	3.00

Table 3
(#8)Keywords still in burst citation status in 2022. The blue line indicates the baseline state, and the red line indicates the period when the burst citation intensity is the highest.

Keywords	Year	Strength	Begin	End	1990 - 2022	Expected lifetime
relapse	2003	3.86	**2017**	2022		2.31
ocrelizumab	2003	15.39	**2018**	2022		11.81
fingolimod	2003	14.03	**2018**	2022		10.69
placebo	2003	11.52	**2018**	2022		8.62
outcome	2003	9.02	**2018**	2022		6.56
childhood	2003	4.5	**2018**	2022		2.84
children	2003	4.38	**2018**	2022		2.74
oral cladribine	2003	3.92	**2018**	2022		2.36
stem cell transplantation	2003	7.69	**2019**	2022		5.47
alemtuzumab	2003	6.65	**2019**	2022		4.61
predictor	2003	3.78	**2019**	2022		2.24
disease-modifying therapy	2003	10.18	**2020**	2022		7.52
network meta-analysis	2003	4.19	**2020**	2022		2.58
adverse event	2003	4.15	**2020**	2022		2.55

To ensure the scientificity and accuracy of keyword prediction, we screened out the keywords that could fully display the outbreak time in the whole table, composed three data sets, and built a model for each set. The lifetime prediction model was visualized in Fig. 7. The model constructed for dataset #6 was (Fig. 7A) $Y = 0.3889*X + 0.7885$, $R^2 = 0.9153$. Asymmetric Sigmoidal, 5 PL, X was log (concentration), Degrees of freedom = 2, $R^2 = 0.9635$ (Fig. 7B), was selected when constructing the model for the dataset of #7. The model constructed for dataset #8 was (Fig. 7C) $Y = 0.8242*$ X-0.8716, $R^2 = 0.9286$. The predicted lifetime corresponding to the keyword was inserted in the last column of.

Tables 1–3

The results in Tables 1–3 for keywords with the burst citation characteristic have an intersection, such as common elements in e-DMT and t-DMT were: safety, and oxidative stress; common elements in e-DMT and I-DMT were: ocrelizumab; common elements in t-DMT and I-DMT were: disease-modifying therapy, oral cladribine; common elements in e-DMT, t-DMT, and I-DMT were: outcome, placebo (Fig. 8).

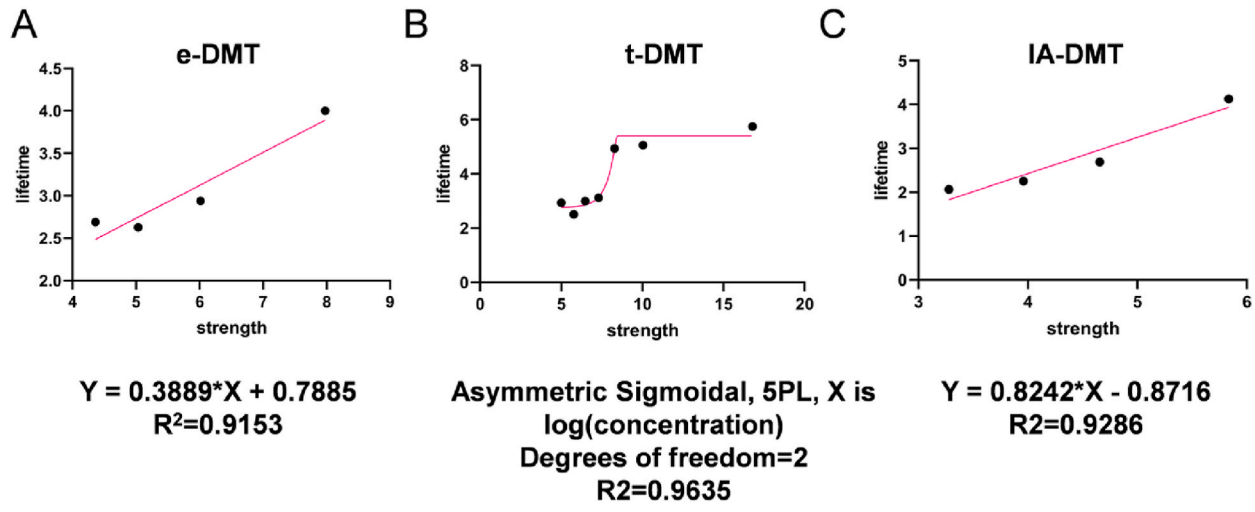


Fig. 7. Prediction model of a keyword lifetime.
We included the keywords with complete burst duration (i.e., keyword lifetime) in the keyword burst citation results as the analyzed database of keyword lifetime, and fitted the model with the largest R^2 by using the data pruning and linear fitting functions in GraphPad, and the model formulas and detailed R^2 values are shown in Fig. The keyword lifetime predicted based on the model with the nature of burst citation is shown in Tables 1–3

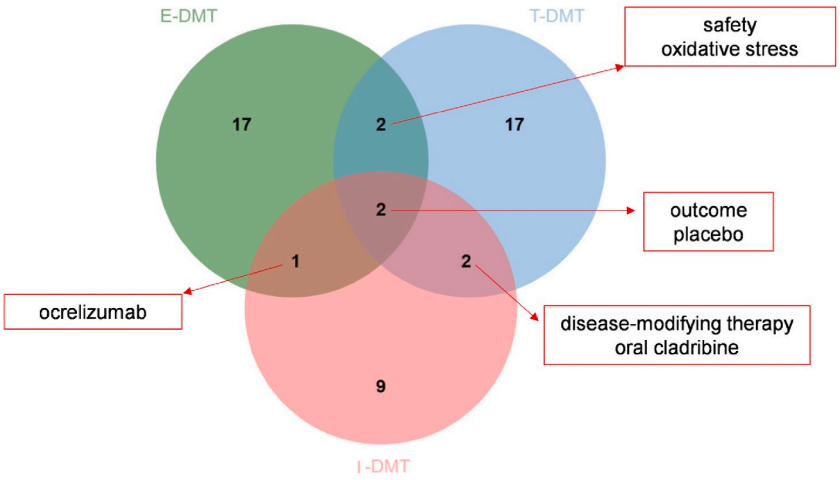


Fig. 8. Venn diagram for keywords with burst citation characteristics.
The Venn diagram is a widely recognized visualization method to find the intersection content of different datasets. We include the keywords with bursty citation characteristics in the three parts of e-DMT, t-DMT, and I-DMT in our analysis, and find that "Placebo", and "Outcome" are the content of the intersection of the three parts.

4. Discussion

We searched PubMed on January 16, 2024, and found no published treatise on bibliometric analysis of MS DMT, thus this paper completely reveals the research lineage of MS DMT and the future direction of MS DMT frontier hotspots, which can help the majority of MS researchers to reacquaint themselves with the large amount of literature on MS DMT from the perspective of data analysis.

Based on the classification of current treatment methods for MS, disease-modifying therapy was analyzed from three angles: e-DMT, t-DMT, and I-DMT. Drugs developed based on conventional therapies, i.e., t-DMT, include the following 13 drugs in this paper: Dimethyl fumarate (DMF) [18–22], Teriflunomide [23–25], Interferon beta (IFN-β) [26,27], Glatiramer acetate [28,29], mitoxantrone [30,31], cladribine [32,33], diroximel fumarate (DRF) [34,35], Ozanimod [36,37], Oral Myelin [38,39], Nanocrystalline gold (CNM-AU8) [40], CS-0777 [41,42], Ibudilast [43,44], Vidofludimus (IMU-838) [45,46]. The drugs classified as part of the emerging disease treatment strategies for e-DMTs were the following 18: Ocrelizumab, Natalizumab, Fingolimod, natalizumab, alemtuzumab, rituximab, ofatumumab, Siponimod, daclizumab, Masitinib, Ublituximab, Evobrutinib, Tolebrutinib, Fenebrutinib, Orelabrutinib,

Daclizumab, Tocilizumab, Amiselimod. As a significant portion of the articles resides in the intersection region of t-DMT and e-DMT, we have also analyzed the corresponding intersection, referred to as I-DMT. In delineating the drug classification of t-DMT and e-DMT at the outset, we also noted a particular class of drugs: antigen-specific agents (ATA-188, ATX-MS-1467, APL for MBP, BHT-3009, Transdermal Myelin Peptides, ETIMS) [47–56], we did not include this section because of its unique therapeutic mechanism. However, antigen-specific agents might be a hot topic for future research due to their ability to alleviate problems associated with long-term immunosuppression (e.g., infections). Even though antigen-specific agents did not show a clear trend in the current literature co-citation and keyword co-occurrence/surge analysis, there were some breakthroughs in developing various prophylactic vaccines for Coronavirus disease 2019 (COVID-19) or therapeutic vaccines for *Mycobacterium tuberculosis* infection in the last years. Particularly impressive with the increasing refinement of gene editing technology along with the development of the CRISPR-Cas9 system. It is believed that there will be a significant breakthrough in antigen-specific agents for MS, and the research hotspots will then inevitably shift from immunotherapy/targeted therapy to the development of relevant therapeutic strategies at the genetic level.

From the overall knowledge context to the analysis of countries, institutions, authors, and journals, then to the co-citation and cluster analysis of reference, and then to the burst analysis of keywords, gradually from the macro perspective of MS treatment to MS possible hot topics in the future. At the same time, this paper used the statistical tool Prism to construct the model of keyword life, which is a new step in the development of bibliometrics. However, all of the above did not manage to be integrated with the actual study content. Therefore, to address this shortcoming, we selected the most frequently cited articles under each topic in the reference analysis (Table S4) for precise reading and further discussion. The analyzed results were carried out in conjunction with the most authoritative MS-related reviews [9–14] of the present day.

From 1991 to 2022, the total number of journals targeted for t-DMT in MS accounted for the most significant proportion among all the DMTs, which was 6521 publications (Fig. 2B). Interestingly, this analysis also found that the USA was the leading country in the field of t-DMT research (Fig. 3B), which had the highest number of publications, with almost twice the publications of Germany (Fig. 3B). As for the e-DMT, it was come up with later than t-DMT. Thus, the total number of publications of e-DMT research was (4142) less than that of t-DMT (6521). Novartis was the major contribution country occupied by the USA and the leading institution. In the I-DMT research field, the USA still played the dominant part, and the leading institution was the University of London. Moreover, since multiple subjects' intersection always comes late, it is worth forgiving the number of publications in I-DMT (1793) less than any other type of DMTs. Notably, the USA was the most significant country with the highest number of publications in DMTs for MS; as for the institution aspect, the University of London played the same vital role in DMTs. The dominance of countries such as the United Kingdom (UK) and the USA and their institutions in MS DMTs is inextricably linked to the hard work of researchers and the number of funding grants [57], the construction of disease-specific databases, and a good journal environment (Fig. 3). We also found that the world ranking of Government budget allocations for Research and Development, which referred to the funding invested by governments to support institutions and scientists, is Japan, USA, Germany, Denmark, France, Italy, Australia, Switzerland, United Kingdom, Canada (https://stats.oecd.org/). According to our analysis of the top 5 countries, the USA was considered the world leader in research and experimentation, despite not being ranked first in government budget allocations for Research and Development. Several factors may contribute to this: Firstly, private sector investment: the USA has a strong tradition of private sector investment in research and experiments, particularly in the technology and healthcare sectors. Secondly, Universities and research institutions: USA has many world-class universities and research institutions that conduct cutting-edge research in a wide range of fields, such as the University of California. These institutions often receive significant funding from both the government and private sector.

From the perspective of institutions, the leader in the e-DMT field was Novartis, a global pharmaceutical and healthcare company, one of the world's top three pharmaceutical companies, headquartered in Basel, Switzerland. This may partially account for why the University of Basel and Switzerland was in the top 5 contributing list. Furthermore, since the University of London is a multidisciplinary federal university combined with various famous universities in London, England could be one of the top 5 countries in all e-DMT, t-DMT, and I-DMT research is not worth doubting.

As for the author, most contributing authors were studying and working in European countries and had various career appointments. In t-DMT research, Comi Giancarlo in Vita-Salute San Raffaele University made a significant difference to t-DMT research and led to Vita-Salute San Raffaele University's excellent reputation in the top 5 institutions. Filippi Massimo and Pozzilli Carlo also worked in Italy and contributed many achievements, which is why Italy and Vita-Salute San Raffaele University can be the top 5 countries and institutions. Moreover, Freedman Mark S could be the most significant contributor to Canada being the top 5 countries. While in the t-DMT research field, German scientists played an essential role. Wiendl Heinz, Gold Ralf, and Hartung Hans-Peter were excellent researchers who made Germany the second leading country in t-DMT. We pointed out that most of the contributing authors were working in Europe. The possible reason may be that European researchers could have more opportunities to cooperate with other laboratories in different countries, such as England, Italy, and Germany, which could help them better communicate the latest research progress.

The analysis of the top 5 journals of DMT in MS showed that the journal *Multiple Sclerosis Journal* had the highest number of publications in the e-DMT and t-DMT field, and the journal *Multiple Sclerosis and Related Disorders* had the highest number of publications in I-DMT. The result may be due to the research of new approaches and methods in the crossover field having a violent impact on the conservative part of the ideas of the long-established journals, so it is relatively tricky for I-DMT to publish in the more classical journals. These data will assist researchers in selecting journals when submitting manuscripts related to MS DMT.

Based on the co-citation of references and cluster analysis, we observed that the topics that still have relevant reference citations in 2022 broadly include the safety of COVID-19 mRNA vaccination (Fig. 4), therapeutic inertia (TI) (Fig. 5), cladribine tablet (Fig. 5), autologous hematopoietic stem cell transplantation (aHSCT) (Fig. 6), progressive MS, pediatric MS (Fig. 6). The fact that the article was cited in relevant references in the more recent past represents that related topics are more likely to be at the forefront of the

ensuing research, and these topics will receive more investigators' attention shortly.

One of the potential frontier topics is the safety of the COVID-19 mRNA vaccine in MS patients. The safety of the COVID-19 mRNA vaccine has been demonstrated in healthy populations, but the role and safety of the COVID-19 mRNA vaccine in patients with autoimmune diseases, such as MS patients, still needs more validation. 2021. Sokratis A et al. studied changes in cellular and humoral immunity in 20 MS patients treated with anti-CD20 therapy and vaccinated with the COVID-19 mRNA vaccine, and compared with healthy individuals receiving the vaccine, MS patients treated with anti-CD20 all produced antigen-specific CD4 and CD8 T cell responses, but the responses of circulating follicular helper T (TFH) cells were reduced, resulting in a lower antibody response produced by the vaccine. This is consistent with the findings of a previous study [58]. Studies on the safety of COVID-19 mRNA vaccine in MS patients using DMT could provide data to assist in clinical and public health decision-making, and with more DMT still to be investigated in addition to anti-CD20 treatment, this topic could become a frontier research trend in the future. It is worth mentioning that our team's achievements in the field of infection prevention, namely the articles related to novel multi-epitope peptide vaccines, have been widely cited [59–62]. Combined with the reality that mRNA vaccines have been awarded the Nobel Prize in 2023, we believe that if MS patient-specific biomarkers can be further explored in the future, vaccines designed against these biomarkers may be a long-lasting and effective therapeutic measure for patients with autoimmune diseases.

The second potential frontier theme is TI, which refers to the failure to initiate or intensify treatment despite evidence of disease activity. Rodrigues et al. conducted a multicenter retrospective observational study of TI events in patients with relapsing remitting multiple sclerosis (RRMS) and found that 1 in 5 patients with RRMS will experience TI. This result confirms the high incidence of TI. TI has been less studied in MS until around 2010 and has maintained some research fervor (Fig. 5B), as investigators have found that studies of TI can be effective in improving clinicians' treatment decisions, leading to the use of DMT or other therapies that are more appropriate for the patient [63].

Another potential class of research frontier is the therapeutic drug cladribine tablet, cladribine tablets represent a selective, highly effective, oral form of immune reconstitution therapy for patients with multiple sclerosis that targets lymphocytes and preserves innate immune cells [64]. Because cladribine is the first oral drug for the treatment of MS and does not require frequent dosing, patient compliance, and dosing experience are significantly enhanced; and cladribine's efficacy has been proven safe and highly effective after validation in phase III trials, with further research focused on long-term disease control and mitigation of adverse events following active treatment, so cladribine research will continue as a potential research hotspot [65].

Similar to cladribine, the research boom in aHSCT began in 2010 and continues through 2022 (Fig. 6B) [66]. AHSCT is a therapeutic method in which the patient's bone marrow, allogeneic bone marrow, or umbilical cord blood is transferred to the patient, and the pluripotent stem cells in the graft settle, proliferate, and differentiate in the body, restoring hematopoiesis and immunity to the patient's organism [66]. Currently, aHSCT has been approved for use in patients with poor response to DMTs and in RRMS patients with poor prognosis, but there is still a relative lack of understanding of the therapeutic principles of aHSCT and comparative trials with DMTs, and therefore further evaluation of the clinical benefits of aHSCT is still needed in the future [66]. Finally, two other frontier topics are progressive MS and pediatric MS, both of which are different subtypes of MS. Trials of DMT in pediatric MS are still ongoing, and data suggest that pediatric MS with DMT delays the onset of disability, but more clinical trials are needed before DMT can be approved for this type [67,68], so the pediatric MS topic has greater promise and enthusiasm for development.

Combined with the Venn diagram of the results of the keyword burst citation analysis, we can find that the keywords of MS DMT suggest two major components: 1. research on underlying mechanisms: pathogenesis with oxidative stress (Fig. 8); 2. clinical aspects: (1) randomized controlled trials (RCTs) evaluation of various drugs/therapeutic measures/different modes of administration of the same drug: e.g. cladribine tablet, aHSCT, ocrelizumab, oral cladribine; (2) RCT for safety assessment of COVID-19 mRNA vaccine injection [65]; (3) Diagnostic/treatment criteria relying on different MS staging/classification/staging.

Shortcomings and limitations: (i) Only English language literature is allowed to be analyzed; further analysis excludes non-English literature; (ii) Only literature from the WoSCC SCIE database is allowed to be analyzed; literature from other databases is excluded; (iii) The classification method of MS DMT is still subject to multiple validations and debates; (iv) Because this paper is the first bibliometric analysis of MS DMT, there is no more appropriate control for comparison; (v) When there is a major event impacting the MS DMT field, such as a major global public health event like COVID-19, further analyses for special periods should be conducted to ensure better specificity of the discussion during such very special periods; (vi) Some cutting-edge articles or research directions may not be captured because they are limited by the number of citations to the article or when they appear particularly close to the point in time when the data were analyzed, such as the effect of brain atrophy on brain damage in multiple sclerosis (brain atrophy in Table 1) [69].

5. Conclusions

This paper comprehensively describes the global research trend of e-DMT and t-DMT separately and collectively. The future research focus for MS DMT is the combination trial or cross-trial of various treatment methods to improve the development of individualized treatment plans for MS patients. The exact contents of the prominent studies include, but are not limited to, ocrelizumab, fingolimod and other monoclonal antibodies, fumaric acid ester, cladribine tablet, aHSCT, and other interventions of RCTs; the impact of mRNA COVID-19 vaccination on MS patients; TI, patient adherence, and other medical management issues; and continued exploration of biomarkers for more accurate disease classification based on the existing clinical indication classification.

Ethics approval and consent to participate

This paper does not include humans or animals involved in the experiment; therefore, there is no need for a permit from the Ethics

Committee.

Consent for publication

Not applicable.

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Data availability statement

All data in this paper are freely available via public databases——Web of Science (https://www.webofscience.com/wos/).

CRediT authorship contribution statement

Fan Jiang: Writing – review & editing, Writing – original draft, Visualization, Software, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Fenghe Zhang:** Writing – review & editing, Writing – original draft, Formal analysis, Conceptualization. **Yue Su:** Investigation, Formal analysis, Conceptualization. **Chao Zhang:** Validation, Supervision, Resources. **Ting Chang:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Project administration, Investigation, 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.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at. https://doi.org/10.1016/j.heliyon.2024.e31744.

List of abbreviations

USA	The United States of America
COVID-19	Coronavirus disease 2019
RCTs	randomized controlled trials
MS	multiple sclerosis
e-DMT	emerging Disease-Modifying Therapy
t-DMT	traditional Disease-Modifying Therapy
\I-DMT	Intersection Disease-Modifying Therapy
WoSCC	Web of Science Core Collection
SCI-E	Science Citation Index Expanded
TS	Topic (includes title/abstract/indexing)
SPMS	secondary-progressive multiple sclerosis
PPMS	primary-progressive multiple sclerosis
RRMS	relapse-remitting multiple sclerosis
MRI	Magnetic resonance imaging
IL	interleukin
GM-CSF	granulocyte-macrophage colony-stimulating factor
TNFα	tumor necrosis factor-alpha
NfL	neurofilament light chain
aHSCT	autologous hematopoietic stem cell transplantation
DMF	Dimethyl fumarate
IFN-β	Interferon beta
DRF	diroximel fumarate

CNM-AU8 Nanocrystalline gold
IMU-838 Vidofludimus
UK the United Kingdom
RRMS relapsing remitting multiple sclerosis.

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