Thematic analysis of multiple sclerosis research by enhanced strategic diagram

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Abstract: Recent interest in multiple sclerosis research warrants literature analysis to evaluate the current state of the discipline and new research domains. This bibliometric review summarised the research trends and analysed research areas in multiple sclerosis over the last decade. The documents containing the term ‘multiple sclerosis’ in the article title were retrieved from the Scopus database. We used Harzing’s Publish or Perish and VOSviewer for citation analysis and data visualisation, respectively. We found a total of 18,003 articles published in journals in the English language between 2012 and 2021. The emerging keywords identified using the enhanced strategic diagram were ‘covid-19’, ‘teriflunomide’, ‘clinical trial’, ‘microglia’, ‘B cells’, ‘myelin’, ‘brain’, ‘white matter’, ‘functional connectivity’, ‘pain’, ‘employment’, ‘health-related quality of life’, ‘meta-analysis’ and ‘comorbidity’. This study demonstrates the tremendous growth of multiple sclerosis literature worldwide, which is expected to grow more than double during the next decade especially in the identified emerging topics.

Keywords: Multiple sclerosis, Harzing’s Publish or Perish, VOSviewer, co-occurrence analysis, thematic analysis, enhanced strategic diagram

Date received: 15 September 2021; revised: 10 December 2021; accepted: 6 January 2022

Introduction
Multiple sclerosis (MS) is an autoimmune chronic inflammatory, demyelinating, and neurodegenerative disease of the central nervous system.1 MS is characterised by inflammation, demyelination, astroglial growth (gliosis) and neurodegeneration.2 Across developed and developing countries, MS prevalence has climbed since 2013.3 MS affects 2.8 million individuals worldwide (35.9 per 100,000 population), with females being twice as affected as males.3 The exact cause of MS is unclear, although a combination of genetic and environmental risk factors is associated with it. Familial MS occurs in roughly 13% of all MS phenotypes.4 MS is polygenic, meaning it is caused by polymorphisms in numerous genes, each of which increases the chance of illness. The HLA class I and II gene polymorphisms are the main risk factors for MS.5 Besides Epstein–Barr virus (EBV) infection during adolescence and early adulthood, other environmental risk factors include lack of sun exposure, low vitamin D levels, and obesity during adolescence.5

Bibliometric analysis is a well-known quantitative method for assessing a corpus of literature in a specific subject area.6 It is getting more popular as a method of determining study trends and patterns.7 The techniques for bibliometric analysis include performance analysis and science mapping.7,8 The contributions of research constituents are taken into account in performance analysis, whereas the linkages between research constituents are the subject of scientific mapping.9 The co-word analysis, one of the science mapping techniques, examines the major topic and essential concepts of a publication. The words are frequently derived from ‘author keywords’, although important words can also be extracted for the analysis from ‘article titles’, ‘abstracts’, and “full texts” in the absence of author keywords for a co-word analysis.9

Recent interest in MS research warrants an analysis of literature review to assess its current state and emerging research fields. Earlier bibliometric analysis on MS was published in 2014.10 The authors examined MS research using articles published in the Science Citation Index-Expanded (SCI-E) database between 2003 and 2012. The authors concluded that there has been a steady increase of MS publications worldwide,
with European countries leading the way (the United States and Canada). Recently, a bibliometric analysis was performed on highly cited MS articles (with more than 100 citations) also using the SCI-E database.\textsuperscript{11} According to the authors, the peak number of highly referenced publications occurred in 2006, with the United States continuing to be the top country and Harvard University ranking first among institutions. Our bibliometric analysis attempted to focus on science mapping to discover main themes and topics based on authors’ keywords co-occurrence analysis, whereas earlier bibliometric analyses focused on performance analysis.

**Methods**

Data involved in this study were retrieved and downloaded from the Scopus database on 3 August 2021. The search term used was ‘multiple sclerosis’ in the article title within the time frame of 2012 to 2021. A total of 26,648 documents were identified and were filtered for source type as ‘journal’, document type as ‘article’, and language as ‘English’. Finally, 18,003 documents were retrieved and downloaded for further analysis (Figure 1). The growth rate in the decade 2012–2020 (percentage change from 2012 to 2020) is calculated as follows: (papers published in 2020 – papers published in 2012/ papers published in 2012) × 100.\textsuperscript{10}

Harzing’s Publish or Perish software was used to perform citation analysis, which used data in RIS format. It provided values for parameters such as TP=total number of publications; NCP=number of cited publications; TC=total citations; C/P=average citations per publication; C/CP=average citations per cited publication; $h=h$-index; and $g=g$-index.

VOSviewer software (1.6.17) was used to map the author’s keywords, which used data in CSV format. It
is a popular application with a simple graphic interface that can be used to build co-authorship network maps of authors, countries, citation analysis, and keyword co-occurrence. This method is especially beneficial for this study since its keyword co-occurrence analysis enables the identification of key research subjects and the detection of major research clusters linked to MS research. VOSviewer supports the introduction of a thesaurus file that can be used for data cleaning by integrating multiple forms of terms (e.g. biomarker and biomarkers, experimental autoimmune encephalitis and eae) to improve the correctness of the analysis. The median values for occurrence, total link strength (TLS) and average publication year were calculated based on the data obtained from VOSviewer.

Theme networks, an overlay network and enhanced strategic diagrams (ESDs) were the three key results of our study. We have plotted the ESDs with the x-axis representing centrality, the y-axis representing density and the z-axis representing time, which is a three-dimensional plane based on a study by Feng et al. The ESDs were then generated by comparing the total link strength (centrality), occurrence (density), and average year of publication (novelty) of each keyword to their derived median values. Based on the plane’s position, four types of themes can be determined.

The degree of interaction between networks is measured by centrality. A theme with a higher centrality score has more external connections to other themes (external strength), thus having a greater impact on the field’s development and evolution. A node having 10 social connections, for example, would have a degree centrality of 10. The higher the centrality score, the more central a topic is within the whole study field under consideration. Thus, the mean strength value of external linkages to other subjects such as TLS was used in this study to determine centrality. The TLS values that were equal or higher than its median value were considered as high while those lower than its median values were considered as low centrality.

In contrast, the density of a topic is used to determine its internal strength or degree of interaction within a network. In this study, co-occurrences of the author’s keywords were used to determine the density. As for centrality, the median value was calculated and the co-occurrence values equal or higher than its median value were considered as high while those below it were considered as low density. The novelty of the topic, however, is represented by time and in this study, the average publication year was used. In terms of novelty, the median value of average publication year was determined, and average publication years equal to or more than its median was deemed novel, while those below it were considered old.

Results

The trend of annual publications from 2012 to 2021
During the 2012–2021 period, 18,003 articles on MS were retrieved from Scopus. In the first 5 years, 44.7% of these articles were published, while 55.3% were published in the second five years (Table 1). There was a steady growth in the number of publications from 2012 through 2018 but rapid growth was observed in 2019. As to date, the highest number of articles was published in 2020 with a total of 7171 citations. Figure 2 shows the evolution of the number of publications and cited publications.

The overall growth rate of publications from 2012 to 2020 was 81.6%. Publications for 2021 was not considered in the calculation because of incomplete data. In terms of the number of cited publications, more than 90% of the articles published between 2012 and 2018 were cited. However, for articles published in 2019, 2020 and 2021, the percentage of cited publications was lower, at 87.8, 67.9 and 25.3, respectively.

Topic analysis based on co-occurrence of author’s keywords
A co-word map was created with a threshold of 60 keyword co-occurrences in VOSviewer. To find themes in the literature, we studied each cluster’s terms. Five themes emerge from the map in Figure 3: animal experiments (22 keywords), neuroimaging (11 keywords), psychosocial rehabilitation (19 keywords), epidemiology (18 keywords) and management (28 keywords). The temporal co-word analysis identifies the publication dates when certain themes were at their most popular. Many newer keywords were identified under cluster 1 (red, management theme) compared to others (Figure 4).

Figure 5(a) depicts the four themes in the novel publication year. These are emerging with high density (upper-left quadrant), emerging with low density (lower-left quadrant), core (upper-right quadrant), and interdisciplinary (lower-right quadrant). Figure 5(b) shows the four themes in the old publication
year, consisting of isolated (upper-left quadrant), obsolete (lower-left quadrant), mature (upper-right quadrant), and declining (lower-right quadrant).

**Discussion**

This bibliometric analysis found 18,003 Scopus-indexed articles published between 2012 and 2021. According to our data, research output increased gradually from 2012 to 2019, then exploded in 2019 and continued to the current year. When compared with the earlier bibliometric analysis on MS,\(^{10}\) the number of articles has almost doubled. Only 9778 articles were published between 2003 and 2012,\(^{10}\) while in almost the same duration, 18,003 articles were published between 2012 and 2021 and this number is expected to increase by end of 2021. Almost in contrast to our findings, a recent meta-analysis that indicated a considerable increase in coronavirus disease 2019 (COVID-19) publications with a significant reduction in non-COVID-19 research.\(^{18}\) This could be explained by several factors. The obvious reasoning is that possibly the doctors and researchers had more time to write and publish papers. Second, some papers focused on MS with COVID-19 also contributed to the mass of published MS papers. Third, the acceptance rates during the pandemic times, especially for COVID-19-related publications were generally ‘more permissive’.

| Year | TP  | NCP | TC    | C/P  | C/CP | C/P  | C/CP |
|------|-----|-----|-------|------|------|------|------|
| 2012 | 1359| 1297| 45,276| 33.32| 34.91| 89   | 143  |
| 2013 | 1574| 1506| 41,785| 26.55| 27.75| 84   | 121  |
| 2014 | 1649| 1566| 39,145| 23.74| 25.00| 76   | 111  |
| 2015 | 1702| 1589| 33,812| 19.87| 21.28| 69   | 106  |
| 2016 | 1770| 1669| 30,845| 17.43| 18.48| 63   | 97   |
| 2017 | 1831| 1697| 27,709| 15.13| 16.33| 53   | 94   |
| 2018 | 1897| 1739| 20,476| 10.79| 11.77| 47   | 71   |
| 2019 | 1978| 1736| 13,952| 7.05 | 8.04 | 36   | 54   |
| 2020 | 2468| 1676| 7171  | 2.91 | 4.28 | 24   | 37   |
| 2021 | 1775| 449 | 930   | 0.52 | 2.07 | 8    | 12   |

TP: total number of publications; NCP: number of cited publications; TC: total citations; C/P: average citations per publication; C/CP: average citations per cited publication; h: h-index; g: g-index.

**Figure 2.** Evolution of the number of publications and cited publications by year.
Figure 3. The main clusters of MS studies based on keyword co-occurrence analysis.
Figure 4. Temporal overlay on keyword co-occurrence map.
Figure 5. Enhanced strategic diagrams showing (a) emerging, core and interdisciplinary in the novel publication year (b) isolated, mature, obsolete and declining topics in the old publication year.
However, the overall growth rate of publications was similar, that is, around 82%.

Science mapping capability to portray the conceptual structure of scientific subjects is unique.\textsuperscript{19} In this study, we found management themes had the highest keywords followed by animal experimentation, neuropsychological rehabilitation, epidemiology, and neuroimaging. This could indicate that MS management research is currently the most popular and has the biggest volume.\textsuperscript{20} Our results identified several core topics in each cluster/theme of MS research. These topics were the most frequent and had strong external links. For example, ‘fingolimod’, ‘disease-modifying therapies’ and ‘safety’ were the core topics under management theme. Many studies related to these topics including drug safety studies were published recently.\textsuperscript{21–23} Under animal experiment theme, ‘multiple sclerosis’, ‘biological marker’, and ‘inflammation’ were the core topics. Biological markers were useful in the context of inflammatory disorders to precisely describe the immune response and prospective therapeutic targets, as well as to better understand the etiopathogenesis and monitoring of disease activity and treatment response.\textsuperscript{24} Specific or latest biomarkers such as ‘neurofilaments’ may not appear as core keywords as they may not exceed the threshold of 60 set for keyword co-occurrence analysis. These biomarkers play a diagnostic role\textsuperscript{25} as well as predict disability progression, monitor ongoing disease activity and assess treatment response in MS.\textsuperscript{26} Under the neuropsychological rehabilitation theme, the core keywords were ‘fatigue’ ‘anxiety’ and ‘exercise’. While new disease-modifying medications are useful in slowing disease progression and neurological decline, there is no effective pharmacological treatment for fatigue.\textsuperscript{27} Physical exercise significantly reduces fatigue\textsuperscript{28} in MS patients, but there is insufficient data support for anxiety.\textsuperscript{29}

The core keywords under neuroimaging theme were ‘cognition’, ‘cognitive impairment’, and ‘brain atrophy’. Cognitive impairment is present in all MS phenotypes,\textsuperscript{30} with a prevalence of 43–70% depending on phenotype and cognitive diagnostic criteria utilised.\textsuperscript{31} Structural correlates of cognitive impairment include white matter and grey matter damage, brain atrophy and network modifications.\textsuperscript{32} Under the epidemiology theme, the core keywords were ‘epidemiology’, and ‘edss’. Expanded Disability Status Scale (EDSS) is a commonly used measure of disability for MS in various studies including epidemiology studies.\textsuperscript{33,34}

The emerging keywords in MS literature include ‘covid-19’, ‘teriflunomide’, ‘clinical trial’, ‘microglia’, ‘b cells’, ‘myelin’, ‘brain’, ‘white matter’, ‘functional connectivity’, ‘pain’, ‘employment’, ‘health-related quality of life’, ‘meta-analysis’ and ‘comorbidity’, while ‘pregnancy’ was the emerging keyword with higher density. These keywords have the potential to expand. For example, COVID-19 has become a major concern for medical professionals across the board including management of MS patients who are often on immunosuppressive drugs. With the pandemic, the therapeutic landscape for MS has shifted, and it will undoubtedly continue to do so in the near future.\textsuperscript{35} While clinical trial and teriflunomide were the emerging topics under management theme, based on the case reports, teriflunomide was safe and used as the first-line treatment for MS patients with COVID-19.\textsuperscript{36}

The emerging keywords in the animal experiment theme include ‘b cells’, which has recently been identified as the main mechanism in the pathogenesis of MS,\textsuperscript{37} and ‘microglial’, which has a role in rescuing oxidised phosphatidylcholines (oxPC)-induced neurotoxicity\textsuperscript{38} in MS. Under the psychosocial rehabilitation theme, the emerging keywords were ‘health-related quality of life’, ‘pain’, and ‘employment’. Various symptoms including pain affect the employment status and quality of life of working-age adults with MS.\textsuperscript{39} Furthermore, according to a recent study, the impact of MS on health-related quality of life (HRQOL) in real-world patients may be underestimated.\textsuperscript{40} A new review also emphasises the need for rehabilitation in fostering daily life involvement in MS patients, as part of a comprehensive plan to address present and future issues.\textsuperscript{40}

‘Brain’, ‘white matter’ and ‘functional connectivity’ were the emerging keywords under neuroimaging theme. Several diffusion magnetic resonance imaging (MRI) studies have found that MS patients have lower structural connectome,\textsuperscript{41} which is best explained by the disruption of long-range white matter tracts\textsuperscript{42} and the disconnection of the major hubs such as the thalamus and nodes of the default-mode brain network.\textsuperscript{43} A functional connection such as resting-state functional MRI (rs-fMRI) was another growing area under this theme and is increasingly being employed to investigate the aetiology of cognitive impairment in MS patients.\textsuperscript{44}

Finally, under the epidemiology theme, the most frequent keywords were ‘meta-analysis’ and ‘comorbidity’. In recent years, comorbidities in patients with MS have piqued researchers’ interest.\textsuperscript{45} Meta-analysis was frequently conducted to pooled epidemiological data such as the worldwide prevalence of MS in specific regions, for example, in Asia and Oceania,\textsuperscript{46} or
in paediatric age group, as well as in other related issues such as suicidal ideation.

There were some limitations to the current analysis. The first was that we employed a single database that does not index all scientific literature and may have left out some significant papers. Second, using our methodological approach, we could only determine the mean occurrence but not the occurrence of each keyword in a specific year. Furthermore, the risk of missing out on some keywords below the minimal number of occurrences that was set was expected and not anticipated to be significant. Third, our methodological approach was unable to identify key external factors that directly impact scientific research. Finally, the number of thematic categories was not formally optimised, and the descriptive themes employed may be interpreted in a variety of ways.

In conclusion, this study has demonstrated a rapid expansion of worldwide literature on MS, with the development trend predicting that it will more than double in size during the next decade. Based on the topic analysis using ESDs, we proposed several emerging research topics under each identified theme, namely management, psychosocial rehabilitation, animal experiment, neuroimaging, and epidemiology, which will likely expand in the near future.

Declaration of Conflicting Interests
The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding
The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The authors would like to acknowledge the Ministry of Higher Education Malaysia for Fundamental Research Grant Scheme with Project Code: FRGS/1/2020/SKK0/USM/02/29 for the financial support.

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