Original Research

High-Mobility Group Box 1 (HMGB1) Protein in Parkinson's Disease Research: A 10-Year Bibliometric Analysis

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Abstract

Background: Parkinson's disease (PD), the most prevalent motoric neurodegenerative disease, has been intensively studied to better comprehend its complicated pathogenesis. Chronic neuroinflammation is a major factor contributing to the development of PD. Reportedly, high-mobility group box 1 (HMGB1) protein is capable of mediating neuroinflammatory response. In this regard, knowledge mapping of the research linking HMGB1 to PD is necessary. **Objective**: Herein, we perform a dynamic and longitudinal bibliometric analysis to explore the hotspots and current trends of HMGB1-related PD publications during the past decade. **Methods**: All PD publications focusing on HMGB1 protein were retrieved from the PubMed database using the search terms "Parkinson's disease" and "hmgb1". Using filters, only English articles published between 2011 and 2022 were selected. The Bibliometrix and Biblioshiny packages from R software were used to conduct the bibliometric analysis. **Results**: The filtered search identified 47 articles (34 original articles and 13 review articles), published between 2011 and 2022. There was an increase trend in the number of articles published, with an annual growth rate of 19.35 percent. In terms of research and scientific collaboration in this field, the United States is in the lead, followed by China, Malaysia, and Australia. Compared to other countries, the United States and China had the highest level of collaboration in this research area. Neuroinflammation, microglia, and receptor for advanced glycation end-products (RAGE) represent the top three frontiers and hotspots for HMGB1-related PD research. According to the thematic evolution analysis, over the last decade, PD, HMGB1 and microglia were addressed individually, however, since 2017, these topics were frequently discussed within the same cluster: neuroinflammation. Furthermore, PD, HMGB1, and neuroinflammation domains co-occurred in majority of the research discussion. **Conclusions**: The link between HMGB1 and PD was realized a decade ago and becomes increasingly important over time. Our findings can aid scholars in comprehending the global context of HMGB1/PD relationship and provide significant insights for future PD research.

Keywords: Parkinson's disease; high-mobility group box 1; bibliometric analysis; neuroinflammation; microglia

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disease involving the loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc). It is associated with motor symptoms, like resting tremor and bradykinesia, and eventually impacts a wide variety of non-motor symptoms, such as sleep disorder and cognitive impairments, as it progresses [1]. Currently, there are more than 10 million reported cases of PD worldwide. According to the World Health Organization (WHO), in 2019, a global estimation of 329,000 deaths was attributed to PD [2]. Furthermore, a data obtained from the Global Burden of Disease 2019 showed increasing trends in the incidence and prevalence of PD from 1990 to 2019 [3]. Besides that, projection analyses estimated that the number of PD patients will continue to increase for the next decades [4,5].

Neuroinflammation plays a major role in the pathophysiology of PD [6]. Although inflammatory response is neuroprotective, however, persistence activation of immune cells, cytokines, and chemokines is neurotoxic and exacerbates neuronal damage [7]. It has been well documented that neurodegeneration in PD is associated with chronic neuroinflammation [8,9]. Despite the evidence, what triggers neuroinflammation and when does it begins in the course of PD still remain largely inconclusive [10].

The high-mobility group box 1 (HMGB1) is a nuclear protein responsible in many cellular processes including DNA repair, transcription, cell differentiation, as well as neuronal development. Evidently, when there is cell damage, this protein acts as damage-associated molecular protein (DAMP) to trigger inflammatory response [11]. Heightened HMGB1 expression levels have been reported in PD patients [12,13]. Inactivating the HMGB1 protein is reported to inhibit neurodegeneration in animal models [14,15]. Besides, some studies have implicated the HMGB1 as one of the potential biomarkers for the diagnosis of PD [12,13,16]. Nevertheless, we are only just beginning to understand the exact role of HMGB1 mechanism in PD neuroinflammation.

Bibliometrics is a branch of analysis that studies the knowledge structure and development of research fields. It is a widely used approach designed to identify the themes, hotspots, and frontiers of a specific research field [17]. This analysis gathers relevant publications within a particular field and quantitatively investigate the past foci, current progress, and its future trends [18]. Although previous bibliometric analyses have explored the connections between PD and neuroinflammation, to our knowledge, no bibliometric analysis linking HMGB1 to PD neuroinflammation has been published. In the current study, we explored the hotspots and current trends of HMGB1-related PD publications in the last 10 years from a bibliometric perspective.

2. Methodology

2.1 Data Sources

Relevant publications were retrieved from the PubMed database using the search terms "Parkinson's disease" and "hmgb1" with publication dates of January 1, 2011, until December 31, 2022. All types of documents, including original articles, reviews, and proceedings were included for the analysis. Using filters, only English articles were selected and used for further analysis. The metadata were downloaded and saved as .csv format.

2.2 Data Analysis

Bibliometrix (http://www.bibliometrix.org) is an R-based package for quantitative bibliometric analysis. Applied together with this package is a web-interface of Bibliometrix, known as Biblioshiny (https://www.bibliometrix.org/home/index.php/layout/biblioshiny). The Bibliometrix package was installed and loaded through R Studio Version 2022.07.2+576 (RStudio, PBC, Boston, MA, USA). Consequently, the Biblioshiny package was loaded by digited "biblioshiny()" command in the R console. The detailed methods and algorithms for both packages were explained elsewhere [19,20]. The downloaded metadata were uploaded on Biblioshiny interface to be analyzed.

Analysis was performed on three factors: general outputs (publication trends and collaborations), publication sources, and authors keywords. In the case of keywords having similar meanings, these words were merged prior to the analysis. Visual outputs from the analysis were downloaded and saved as .png format.

3. Results

3.1 Analysis of Publication Outputs, Growth Trends, and Scientific Collaborations

As summarized in Table 1, the analysis identified a total of 47 relevant articles that linked HMGB1 to PD development, published between 2011 and 2022 (the list of articles is provided in **Supplementary Material**). These articles were published in 36 different publication sources, mainly journals. Over the last decades, publication growth

Table 1. Main information of the selected articles gathered by Biblioshiny.

Description	Results
Documents	47
Timespan	2011–2022
Publication sources	39
Authors	275
Co-authors per document	6.66
Authors keywords	445
Annual growth rate (%)	19.35

rate was 19.35% and 2021 marked the highest number of publications (Fig. 1). A total of 275 authors from various countries, such as the United States, China, Malaysia, and Australia, participated in this field of research and the average number of co-authors per article was around six to seven individuals. In terms of the scientific collaborations, the most frequent collaboration was between authors from the United States and China (Fig. 2).
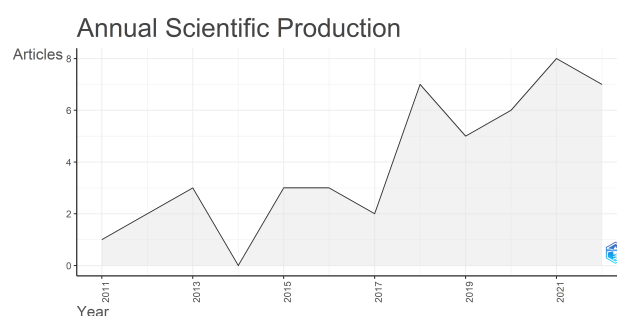

Fig. 1. The total number of annual publications. The year 2021 had the most publications between 2011 and 2022, with eight articles published.

3.2 Analysis of Publication Sources

Bibliometric analysis identified a total of 39 journals published HMGB1-PD articles from 2011 to 2022. The top 10 journals publishing articles in this research field are presented in Fig. 3. The *Life Sciences* journal was the highest journal on HMGB1-PD research with four articles (8.51%), followed by the *Autophagy* journal with three articles (6.38%), as well as the *Biomedicine & Pharmacotherapy*, *Neurobiology of Disease*, and *Neurotoxicity Research* journals with two articles each (4.23%) (Fig. 3). According to the Bradford's Law of Scattering, the core sources for this research field are *Life Sciences*, *Autophagy*, *Biomedicine & Pharmacotherapy*, *Neurobiology of Disease*, *Neurotoxicity Research*, *ACS Chemical Neuroscience*, *Acta Pharmaceutica Sinica B*, and *Anticancer Research* (Fig. 4).
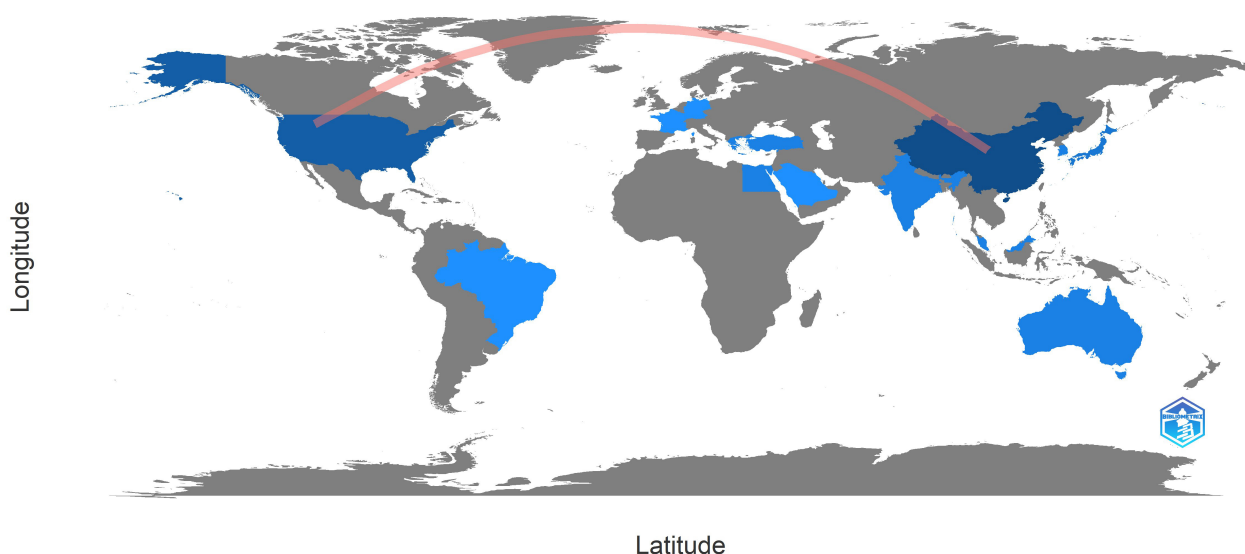
Country Collaboration Map

Fig. 2. Scientific collaboration world map. Countries with a darker blue shade have a higher number of publications. The red line connects the two countries with the highest frequency of collaboration.
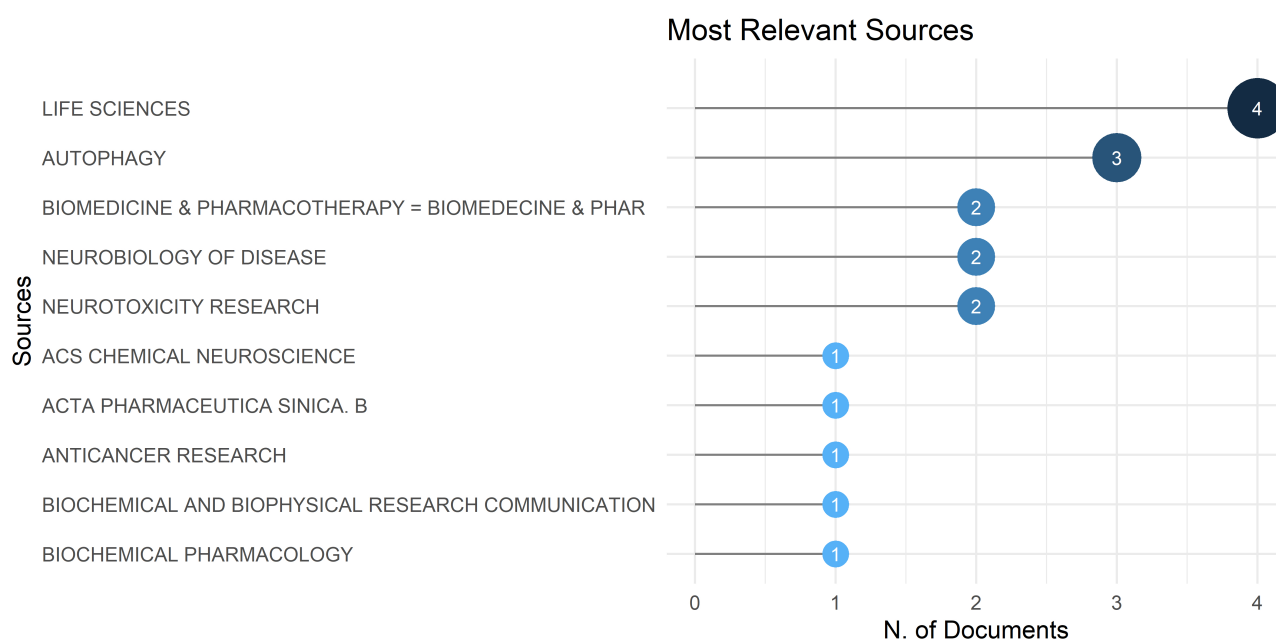

Fig. 3. Top 10 journals that published HMGB1-PD related articles from 2011 until 2022.

3.3 Analysis of Keywords

Keywords assigned by the authors in their articles are especially useful for bibliometric analysis when investigating the hotspots and trends of a specific research field. By performing keyword analysis, we revealed top 10 most frequent keywords used by the authors for the HMGB1-PD research (Fig. 5). Of 445 keywords, "HMGB1" and "Parkinson's disease" were used most frequently, both with 24 occurrences, followed by "neuroinflammation" with 19 occurrences. Several keywords related to PD neuroinflammation and neurodegeneration, including "microglia", "autophagy", "RAGE" and "α-synuclein", were also identified as frequent words, with nine, eight, and five occurrences respectively. In parallel with the upward publication trend, cumulative occurrences of the keywords also increased (Fig. 6). The most noticeable increments are "HMGB1" and "Parkinson's disease" with over 20 cumulative occurrences out of 47 analyzed articles.
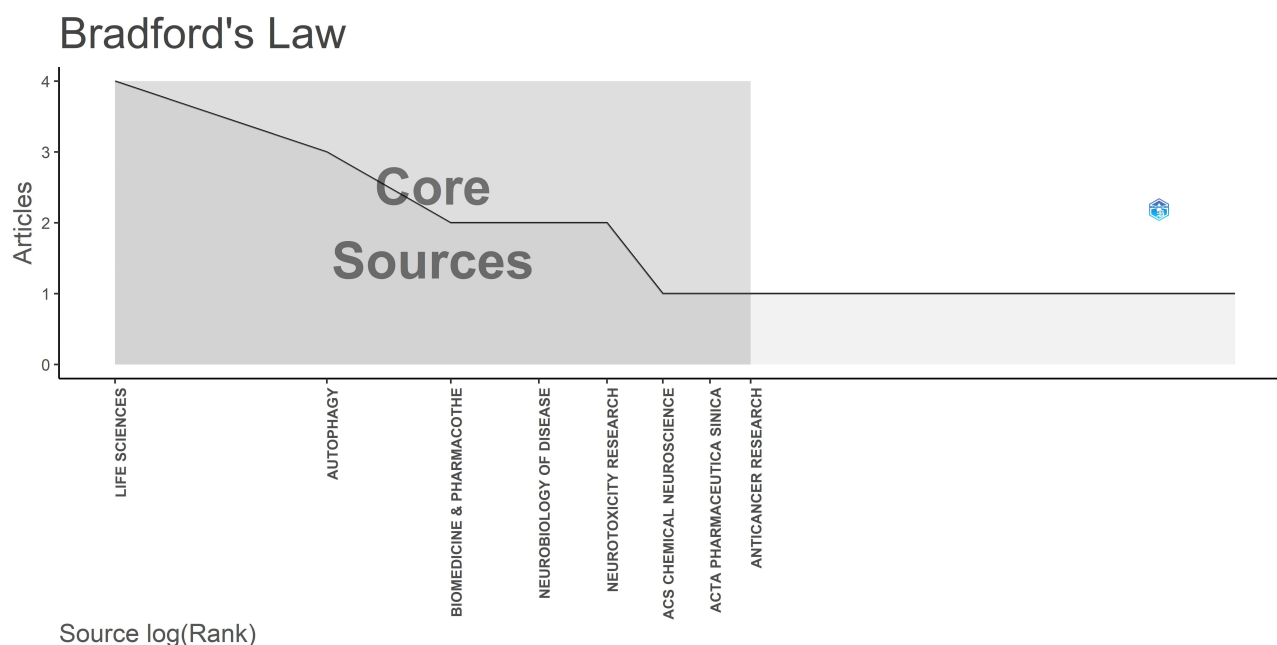
Fig. 4. Core publication sources clustering through Bradford's Law.

Fig. 7 presents the co-occurrence analysis of keywords that shows the network of top 50 keywords. Node sizes reflect the frequency of keywords while node colors indicate clusters and the correlation between nodes. After the analysis is complete, the keywords are divided into 3 main clusters, illustrating the factors used to divide the keywords and which criteria were considered. The red cluster is the largest one and with the most nodes. This cluster includes PD-related terms such as "Parkinson's disease", "tyrosine hydroxylase", and "α-synuclein", as well as HMGB1-related terms such as "HMGB1", "MPTP", and "paraquat". The blue cluster includes "neuroinflammation", "microglia", "RAGE", and "astrocytes", all of which are related to neuroinflammatory response. Meanwhile, the purple and green clusters are mechanically related to neurodegenerative diseases and PD development, respectively.

Analysis of the thematic evolution identifies the shifts and changes in research discussion over the years. The current study analyzed the evolution of hotspots and foci of HMGB1-PD research, with 2016 as the middle cutting year. Referring to the thematic evolution framework in Fig. 8, it can be inferred that in the early years (2011–2016), PD, HMGB1, and microglia were categorized individually and in different clusters. Besides, researchers were most interested in discussing autophagy when it comes to relating HMGB1 with PD pathogenesis. On the contrary, in more recent years (2017–2022), the clusters were evolved and fused into one cluster: neuroinflammation, and surpassed autophagy as the main interest in discussing HMGB1-PD research.

4. Discussion

Parkinson's disease places a heavy burden on the quality of life of patients and the caregivers [21]. Mechanistically, the expression of HMGB1 protein is reported to be upregulated in the brain of PD patients [22,23] and animal models of PD [12,24]. Since the activation of HMGB1 protein triggers neuroinflammatory response [11,25] and chronic neuroinflammation is a major factor of PD pathophysiology [6,26], the link between HMGB1 protein and PD pathogenesis should be realized.

To the best of our knowledge, this is the first bibliometric analysis of research on the link between PD and HMGB1 protein. General overview of the analysis showed an upward growth trend of relevant publications over the last 10 years. Increases in the number of articles over the past decade provide evidence of the continuous growth in interest in this research field. Strikingly, we did try to perform a 30-year bibliometric analysis, however, the earliest article discussing the link between HMGB1 and PD was published in 2011. Therefore, it is tempting to speculate that the connection between HMGB1 and PD has only been realized 10 years ago. Although still in its early period, this field of research continues to grow and becomes increasingly important over time.

The majority of HMGB1-PD research articles originated in the United States and China, indicating the significance of both countries in PD research. Other countries, including Japan, Australia, India, and Malaysia, have also contributed to this research field. It is fair to assert that the link between HMGB1 and PD has piqued the interest of researchers from both developed and developing countries. Also, Malaysia has announced the Science and Technology
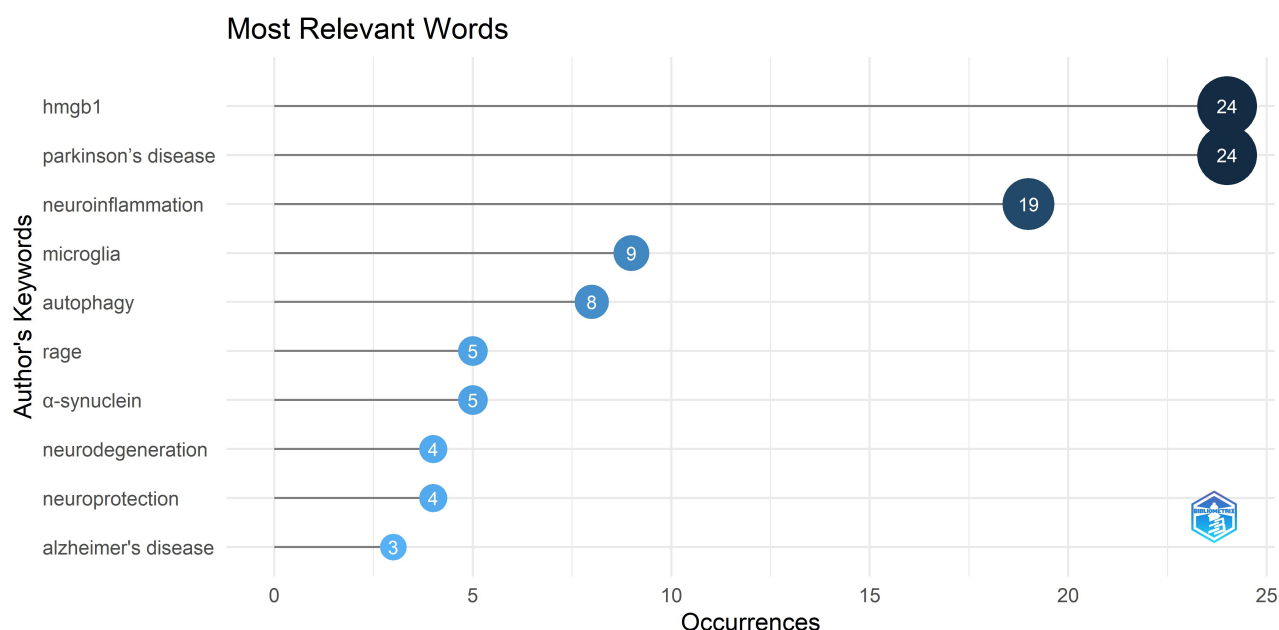
Most Relevant Words

Fig. 5. Top 10 most frequent keywords used by authors for their HMGB1-PD articles.
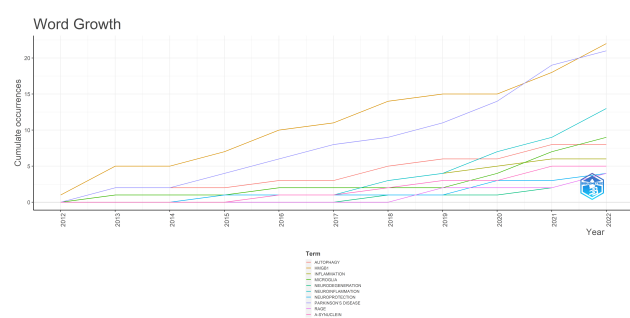

Fig. 6. Cumulative keyword occurrences from 2012 to 2022.

Foresight 2050 initiative, one of the goals of which is to construct and develop neuro-technologies [27], resulting in a surge in interest in neurodegenerative disease research.

Academic journals are the main source of cutting-edge knowledge and a place to publish research findings of a particular field. From the analysis of publication sources, we identified 39 journals that have published HMGB1-PD articles. Of the 39 journals, the *Life Sciences* journal published the highest number of articles in this field followed by the *Autophagy* journal. Both journals are Q1 journals, with impact factor (IF) of 6.78 and 16.02, respectively. *Life Sciences* is a scientific journal covering research on the molecular, cellular, and physiological mechanisms of pharmacotherapy, whereas *Autophagy* focuses on all aspects of cell autophagy and its connection with human health and diseases. In addition, we utilized Bradford's Law of Scattering to assess the core publication sources. This law implies that, for any research field, the core (Zone 1 out of 3) reflects the journals that are most frequently mentioned in the publications of that field and are most likely to be of the

greatest interest to researchers in that field [28]. The core sources for this research field are the two aforementioned journals, *Biomedicine & Pharmacotherapy*, *Neurobiology of Disease*, *Neurotoxicity Research*, *ACS Chemical Neuroscience*, *Acta Pharmaceutica Sinica B*, and *Anticancer Research* journals. The most recent quartile for all journals except *Anticancer Research* is Q1, and the IFs range is between 3.5 to 16.02. The analyses show that most articles describing HMGB1-PD research are published in reputable, indexed journals with a high reputation. Based on the nature of these articles, it can be inferred that research on HMGB1 and PD is multidisciplinary focus, with a concentration on neurology and pharmacology.

Authors of each published article are required to provide at least five keywords that summarize the main point of their work. Analysis of these keywords can give useful information about the trends in a particular research field. Apart from "HMGB1" and "PD", "neuroinflammation", "microglia", and "autophagy" were among the most frequently used keywords in the field of HMGB1-PD research. Being regarded as a prominent contributor to the pathogenesis of PD, neuroinflammation has far-reaching consequences for brain health and function of the central nervous system (CNS) [29]. A key cellular mediator of neuroinflammatory processes is the activation of a resident immune cell in the brain known as microglia [30]. Notably, "microglia" was another frequently used keyword in this research field and reflect a trend in research linking HMGB1 expression with microglial activation. Although microglia have an important neuroprotective role, prolonged and excessive microglial expression has negative effects on the brain [31]. Accumulating evidence re-
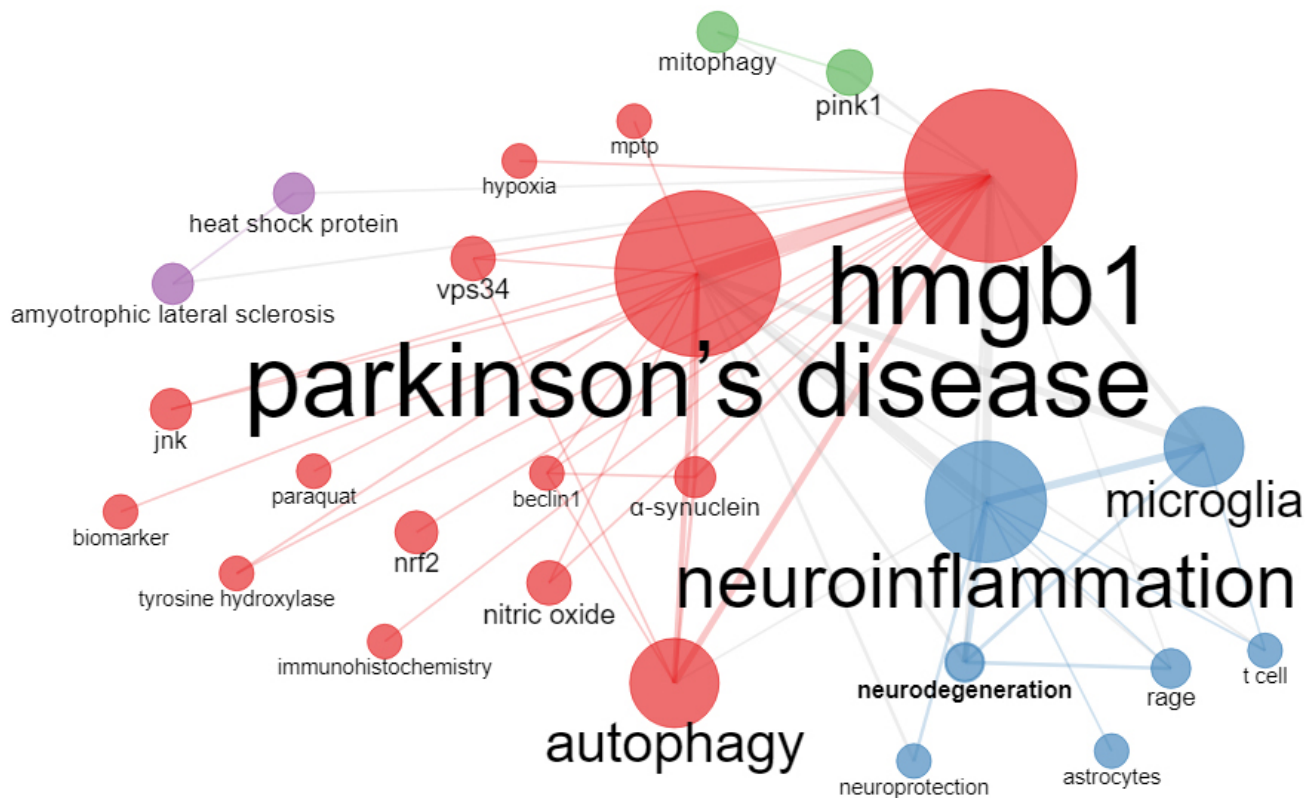
Fig. 7. Co-occurrence network of the topics discussed. Nodes with the same color indicate topics under the same cluster.
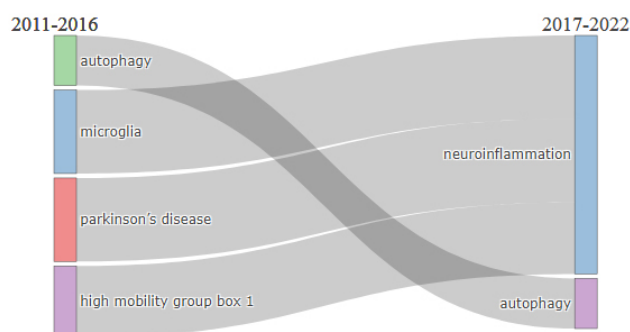

Fig. 8. Thematic evolution over the decade. The figure depicts the evolution of hotspots and trends of HMGB1-PD research with 2016 set as the middle cutting year.

ported overexpression of microglia in the brains of PD patients [32,33]. Microglia become activated following exposure to pathogen-associated molecular patterns (PAMPs) and DAMPs [34]. Once released into the extracellular matrix, the HMGB1 proteins act as DAMPs that can activate microglia and downstream RAGE and Toll-like receptor 4 (TLR4) signalling [35]. Furthermore, microglia perform autophagy process to engulf neuron-released α-synuclein for degradation. Autophagy dysfunction and α-synuclein accumulation widely contribute to PD development and pathophysiology [36]. Markedly, "RAGE", "autophagy" and "α-synuclein" were among the top keywords used in the HMGB1-PD research. Moreover, the analysis

of these keywords showed upward cumulative occurrences over time, suggesting that the discussion on related topics is still relevant and on-going.

Large clusters in keyword co-occurrence networks indicate core research hotspots. Based on our analysis, apart from HMGB1-PD related topics, the hotspots for this research also include neuroinflammation-related topics. This implies that, when discussing the connection between HMGB1 and PD, researchers focused on neuroinflammatory mechanisms. HMGB1 proteins are proinflammatory since its release into the extracellular matrix serve as DAMPs that consequently trigger inflammatory responses [35]. According to Ren *et al*. [15], knowledge of HMGB1 bridges the gap between chronic neuroinflammation and dopaminergic neurodegeneration in PD pathophysiology. Furthermore, the thematic shift in focus of HMGB1-PD research from individual discussion (HMGB1, PD, and microglia) to integrated focus (neuroinflammation) suggested that researchers have gained more knowledge towards understanding the pathophysiological mechanisms of PD. Individual focus on each topic in the early years implies that the trends of HMGB1-PD research were fundamental and less focused on the connection between the topics. Since 2017 onwards, the focus has evolved to finding the link between PD, HMGB1, and microglia through neuroinflammatory mechanisms, indicating a more sophisticated and complex discussion.

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5. Limitations

Notwithstanding its implications for research, this bibliometric analysis had limitations. First, the selected articles were only from the PubMed database, consequently, the results of this analysis were only applicable to this criterion. Combining papers from additional sources, such as Web of Science and Scopus, may yield more comprehensive results. Second, the analysis excluded all publications written in languages other than English. Incorporating multilingual articles is difficult due to the need for a thorough pre-analysis screening to accurately merge synonym keywords. However, it is intriguing to have articles written by researchers of different natives, as this may reveal insights from many angles.

6. Conclusions

Parkinson's disease is a major health issue, particularly for the elderly, because it affects both physical and mental health. In this current study, we introduced a decade of research on PD and its connection with pro-inflammatory HMGB1 proteins. We provided a detailed overview of HMGB1-PD research and shown that it is a promising and expanding topic of study. The bibliometric analysis of HMGB1-PD research has shown growth increment in the number of relevant publications during the past 10 years. The US and China were the most active participating countries, while the *Life Sciences* and *Autophagy* journals were the most active sources of publication for this research filed. Keyword analysis results identified "Parkinson's disease", "HMGB1", "neuroinflammation", "microglia", and "autophagy" as the top five most frequently used keywords that reflect current hotspots and prospective future paths in this field of research.

Availability of Data and Materials

All data generated or analyzed during this study are included in this published article.

Author Contributions

KR and WMYM participated in study design. KR performed the analysis and manuscript preparation. WMYM contributed to the overall outcomes of the analysis and helped revise the manuscript. Both authors contributed to editorial changes in the manuscript. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Conflict of Interest

The authors declare no conflict of interest. WMYM is serving as one of the guest editors of this journal. We declare that WMYM had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Gernot Riedel.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/j.jin2204087.

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