

New Trends and Hot Spots in the Study of Diabetic Peripheral Neuropathy: A Bibliometric Analysis

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Abstract: Objective: Diabetic Peripheral Neuropathy (DPN) is a common chronic complication of diabetes that currently has no therapeutic recourse. Advanced DPN stages are characterized by severe symptoms that place a huge burden on patients and healthcare systems. To the best of our knowledge, research hotspots within the field of DPN are yet to be visually analyzed, and so is the exploration of developmental dynamics within the same discipline. **Methods:** Herein, DPN articles published between 2002 and 2022 were retrieved from the Web of Science Core Collection database. Following that, bibliometric analysis was performed on these articles using CiteSpace, VOSviewer, Microsoft Excel, and R-bibliometrix tools. **Results:** We retrieved 2,761 DPN articles involving 11,605 researchers from 1,140 institutions in 99 countries/regions. The United States was the country/region with the highest number of publications. The most productive author was Malik Rayaz A from the University of Manchester, which was the most productive institution. The most co-cited journals were Diabetes Care, Pain, and Neurology. On the other hand, #0 neuropathic pain, #1 neuropathic pain treatment and #2 peripheral neuropathy were the most clustered keywords in co-cited references. Based on the clustering of keywords, timeline graphs, and citation bursts, “risk”, “corneal confocal microscopy” and “systematic review” were identified as the key issues for future DPN research. **Conclusion:** This article summarizes the current DPN research status and focus areas, reveals the future development trend, and points out potential research directions for DPN scholars.

Keywords: Diabetic Peripheral Neuropathy; Bibliometric Analysis; VOSviewer; CiteSpace; R-bibliometrix

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1.Introduction

With its continuously growing prevalence worldwide, Diabetes Mellitus (DM) is one of the major public health problems in the 21st century ^[1]. Surveys have revealed that almost half of diabetic patients are unaware of their condition ^[2], exposing them to numerous acute and chronic complications as the disease progresses. Diabetic Peripheral Neuropathy (DPN), a common chronic diabetic complication, has symptoms linked to peripheral nerve dysfunction that severely affect patients' Quality of Life (QoL) and places a heavy burden on physicians and healthcare systems ^[3]. The International

Diabetes Federation (IDF) regularly publishes the Diabetes Atlas report, providing the most up-to-date information on the epidemiology and associated impact of diabetes worldwide. This publication has influenced the awareness levels and importance of diabetes among governments, policymakers, researchers, and the general public. Diabetes foot-related complications such as DPN were examined in greater depth in the IDF Diabetes Atlas 2022 Reports, and available information suggests that DPN prevalence is higher in Africa, and South and Central America, with one study in Senegal discovering that 72% of diabetes patients had DPN^[4]. The growing DPN prevalence as predicated by the rising population of diabetic patients, necessitates more DPN research.

Although the pathogenesis of DPN remains unclear, the development and progression of diabetic complications such as DPN have been associated with insulin resistance, hyperglycemia, and dyslipidemia, along with abnormalities in the metabolism of nonessential amino acids^[5]. In a high-glucose environment, Schwann cell-derived exosome miR-21 may be involved in nerve growth regulation and, thus, DPN progression via the AKT signaling pathway^[6]. Previous clinical research has shown that serine and glycine levels are lowered in metabolic syndrome patients and that systemic serine and glycine reduction is linked with impaired vision and peripheral neuropathy^[7-8]. Furthermore, recent research has revealed the serine deficiency mechanism; serine deficiency accelerates DPN by regulating sphingolipid metabolism, and dietary serine supplementation can alleviate DPN^[9]. As a result, serine-based modulators may be a novel therapeutic avenue for DPN treatment. Additionally, a recent study revealed that intestinal flora-mediated DPN pathogenesis could be associated with intestinal barrier dysfunction, antigenic load, and the exacerbation of systemic inflammatory responses, and through Random Control Trials (RCTs), it also demonstrated that colony transplantation targeting intestinal flora could be a new strategy for treating DPN^[10]. Despite promising research findings on the epidemiology and pathogenesis of DPN, there is still no medical recourse to prevent DPN or manage its symptoms. Glycemic control, nutritional supplementation, and anti-oxidative stress, which are effective in early-stage patients but less effective in reversing severe symptoms in advanced stages of the disease, are the primary DPN therapies^[11].

Given its significant clinical challenges, DPN remains a research focus among scholars in various countries and regions. In recent years, relevant bibliometric assessments have been conducted in several areas with high diabetic prevalence. However, there is no bibliometric analysis specifically for DPN. Furthermore, existing DPN studies have only addressed peripheral neuropathic pain symptoms in diabetes, with the literature summarized limited to the 2011-2021 decade^[12]. Therefore, this study visualized the number of DPN research articles, authors, countries/regions, institutions, references, and keywords between 2002 and 2022 using bibliometric analysis to summarize the current DPN research status, identify focus areas, and explore the future development trend, ultimately highlighting valuable research directions for DPN scholars.

2. aterials and methods

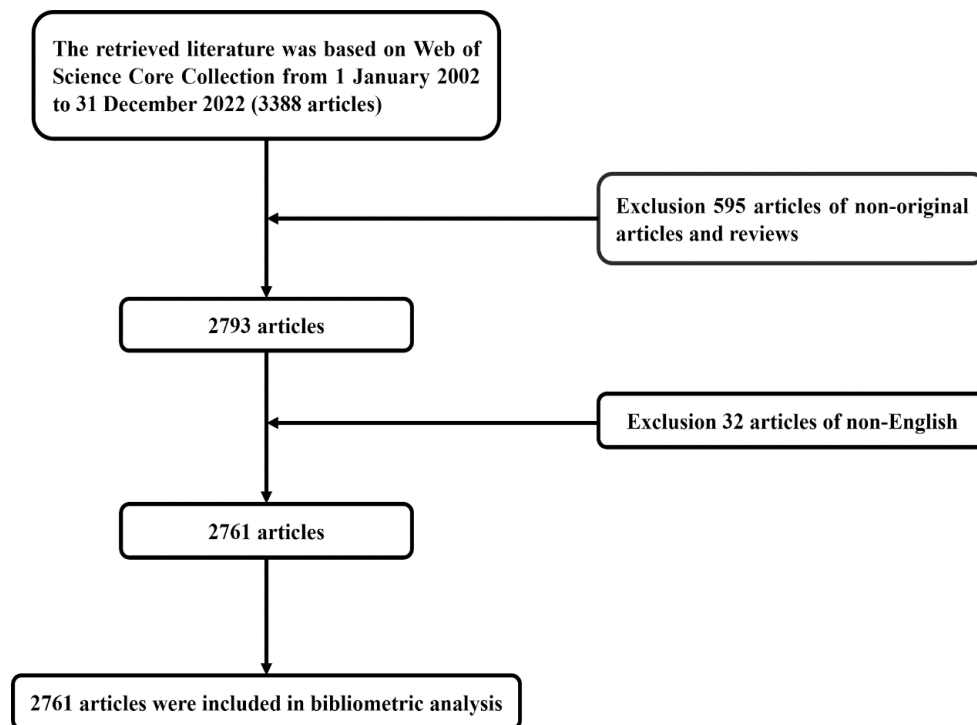
2.1 Literature sources and search strategies

We searched the Web of Science Core Collection (WOSCC) database for DPN articles published between 2002 and 2022. The search strategy was: TS="diabetic peripheral neuropathy" OR "diabetes peripheral neuropathy" OR "diabetic peripheral neuropath". Data retrieval was completed on October 11, 2023, to ensure the accuracy of the results. Article type was limited to original articles and reviews, whereas language was limited to English. After strict screening, the study data were exported for software analysis (Fig.1).

2.2 Analysis methods

Data were analyzed and visualized using CiteSpace 6.1.6, VOSviewer 1.6.18, Microsoft Excel 2021, and R (version 4.3.1) package "bibliometrix" (<https://www.bibliometrix.org>). Specifically, detailed information on the articles' country/region of origin, authors, references, and keywords were analyzed using CiteSpace^[13] and VOSviewer^[14-15]. On the other hand, we analyzed the articles' average annual citations using the R-bibliometrix package, and presented a map of the distribution of postings by country/region and a graphical representation of the authors' posting volume through time-varying relationship mapping. Furthermore, we constructed a trend graph of the number of articles issued and the average yearly citation using Microsoft Excel 2021, and presented a quantitative visualization of multiple data.

Fig. 1 Flowchart of the literature data screening process.

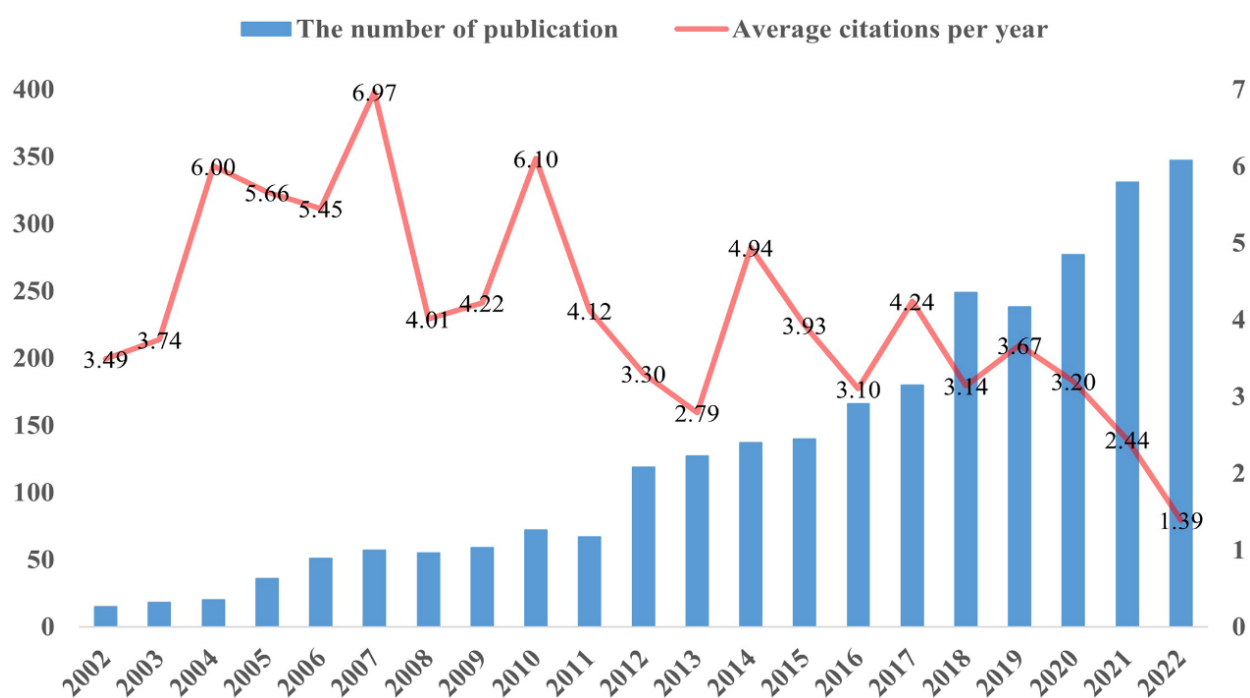


3.Results

3.1 Annual publication and citation trends

Our search for DPN-related research in the WOSCC database yielded 2,761 articles. The trend of annual DPN publications and citations was in two phases: 2002-2011, which is the early stage of research with < 100 publications per year, and 2012-2022, which is the period of significant growth in DPN research, with the number of publications in 2022 (n=347) being approximately three times that in 2012 (n=119) (Fig. 2). Regarding the average annual citations, 2007 had the highest average (6.97), while both 2004 and 2010 had an average > 6, which could be attributed to the fact that there were fewer DPN studies between 2002 and 2011. These results indicate that DPN studies gained momentum over the last decade and continue to interest researchers.

Fig. 2 Trends in the number of publications and average citations per year.



3.2 Countries/regions and institutions

We found that 1,140 institutions from 99 countries/regions contributed to DPN research. The United States and China led the first tier of countries in the number of articles published in each country/region with 844 and 695 articles, respectively (Fig. 3A), followed by the United Kingdom, India, and Germany, which had 274, 141, and 105 articles, respectively (Table 1). Notably, the mediational centralities of the United States and the United Kingdom were much higher compared to other countries at 0.59 and 0.37, respectively. The mediational centralities of the remaining countries were all < 0.1 . We constructed the cooperation network of the top 20 countries/regions based on the number of articles issued using VOSviewer (Fig. 3B). Although China had a higher number of published articles and collaborations with most countries, the United States and the United Kingdom were more closely related to the countries they collaborated with. Notably, the UK had the most collaborations with US, Qatar, Australia, and Italy despite having the third-highest volume of publications.

Of the 1,140 institutions, 99 with ≥ 10 publications were analyzed to generate an institutional collaboration network map showing eight clusters (Fig. 3C). The University of Manchester in the UK came in first with 108 articles (Table 2), and it mainly collaborated with the UK-based Manchester Metropolitan University and the Qatar Foundation University in Qatar, among others. Although Pfizer Incorporated was not the most prominent organization regarding the number of articles published, it had the largest cluster. Furthermore, besides collaborating with institutions in its cluster, Pfizer Incorporated collaborated with institutions in the other four clusters. Pfizer Incorporated published 200 diabetes-related original articles or reviews between 2002 and 2022, with DPN accounting for 47.5% (95/200) of all its publications, implying that the company has invested substantially in developing DPN treatment drugs. The University of Manchester and Pfizer Incorporated were followed by the University of Michigan (US), Shanghai Jiao Tong University (China) and Fudan University (China), which had 62, 46, and 38 publications, respectively.

Table 1 Top 20 countries/regions by number of articles.

Rank	Country/region	Records	Centrality	Rank	Country/region	Records	Centrality
1	USA	844	0.59	11	Qatar	70	0.03
2	China	695	0.08	12	Iran	63	0.04
3	England	274	0.37	13	Turkey	63	0
4	India	141	0.03	14	Netherlands	57	0.03
5	Germany	105	0.07	15	Spain	50	0
6	Canada	95	0.02	16	France	48	0.05
7	Japan	95	0.03	17	Taiwan	48	0.01
8	Italy	93	0.07	18	Brazil	45	0.02
9	Australia	89	0.04	19	Egypt	44	0.04
10	South Korea	79	0	20	Saudi Arabia	39	0.02

Table 2 Top 20 institutions by number of articles.

Rank	Institution	Records	Rank	Institution	Records
1	University of Manchester	108	11	Johns Hopkins University	31
2	Pfizer Incorporated	95	12	University of Calgary	28
3	University of Michigan	62	13	Capital Medical University	28
4	Shanghai Jiao Tong University	46	14	Weill Cornell Medicine - Qatar	27
5	Fudan University	38	15	Nanjing Medical University	27
6	University of Rochester	37	16	University of Miami	26
7	Manchester Metropolitan University	36	17	Southern Medical University	26
8	University of Kansas	36	18	Chinese Academy of Medical Sciences	26
9	University of Washington	35	19	Qatar Foundation	25
10	Queensland University of Technology	33	20	University of Oxford	25

A

World map showing the number of COVID-19 research nodes per country. The USA and China are the most prominent nodes, indicated by a dark blue color. A legend at the bottom left shows a color scale from 1 to 844. A logo is in the bottom right.

B

Network visualization of countries. Nodes represent countries, and edges represent research connections. The USA and China are central nodes, connected to many other countries like Japan, England, Canada, and Australia.

C

Network visualization of research institutions. Nodes represent institutions, and edges represent research connections. Key institutions like Pfizer Inc, Univ Manchester, and Univ Michigan are prominent.

The authors of the 2,761 articles were analyzed, yielding 11,605 researchers involved in DPN research, including 23 authors with ≥ 10 publications. Additionally, author collaborations across the 2,761 articles were analyzed using CiteSpace yielding 790 nodes and 1,458 links. Node sizes correlated with the number of publications for each author, with different node colors indicating different publication dates, and warmer and cooler colors representing more recent years and more distant years, respectively (Fig. 4A). The collaborative network shows that Malik Rayaz A (as the center) worked closely with Petropoulos Ioannis N, Alam Uazman, Ponirakis Georgios, Khan Adnan, Efron Nathan, Boulton Andrew J M and other researchers in the last three years. Notably, although Parsons Bruce had many publications and several collaborations with Emir Birol and other researchers, their studies were primarily conducted before 2020.

We analyzed the top 20 authors using the “bibliometrix” R package (version 4.3.1) to explore the relationship between authors’ publication volume and time change. We constructed a graph in which node sizes on the line represented the number of articles published by the authors each year and node colors represented the total number of citations of the authors’ articles each year, with darker (color) dots indicating more citations (Fig. 4B). Compared to other years, the number of publications by most authors increased significantly in 2021, with nine researchers publishing $\geq$ five articles (Fig. 4B). Malik Rayaz A was the author with the highest number of publications with 64 total citations (Fig. 4B). Interestingly, Marshall Andrew had

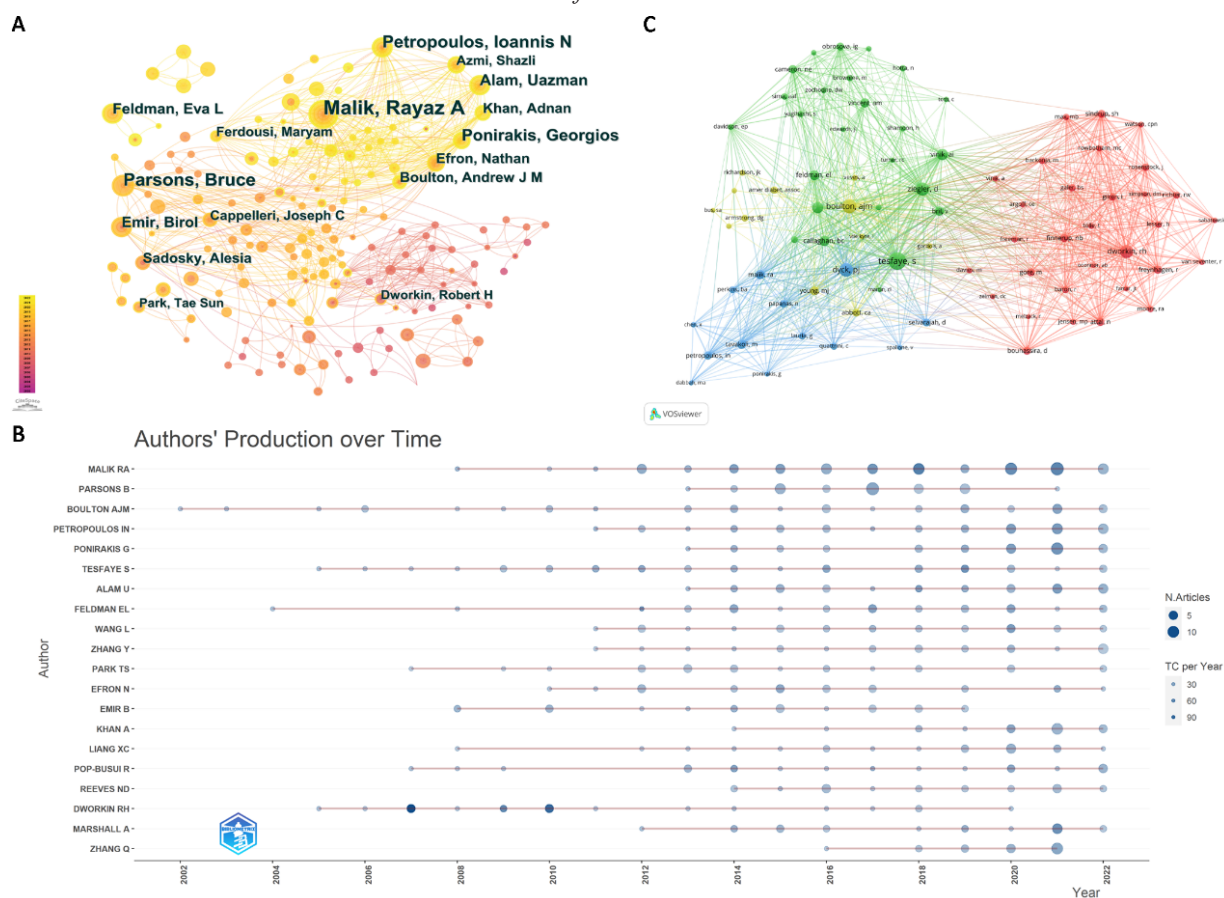
the highest total number of citations for each publication year with 118 and 91 total citations in 2007 and 2010, respectively, corroborating the average annual citation results illustrated in Figure 1.

We analyzed the co-cited authors through VOSviewer, which yielded 48,235 co-cited authors, of which the top ten authors were all cited > 300 times (Table 3). Prof. Tesfaye S from the British Sheffield Teaching Hospitals NHS Foundation Trust, Academic Unit of Diabetes and Endocrinology, was the top-ranked author, having published more review articles on pathogenesis, disease diagnosis, screening, and early intervention to summarize and evaluate DPN research [16-17]. Boulton AJM and Dyck PJ were ranked second and third, respectively. We analyzed 81 authors with ≥ 100 co-citations using the strength of association algorithm to generate an author co-citation network map (Fig. 4C). These co-cited authors were clustered into four categories based on their strong associations with four researchers: Tesfaye S, Boulton AJM, Dyck PJ, and Dworkin RH (Fig. 4C).

Table 3 Top 10 authors by number of articles and top 10 authors by number of co-citations.

Rank	Author	Records	Rank	Author	Records
1	Malik Rayaz A	64	1	Tesfaye S	1119
2	Parsons Bruce	38	2	Boulton AJM	749
3	Petropoulos Ioannis N	29	3	Dyck PJ	692
4	Ponirakis Georgios	28	4	Dworkin RH	648
5	Alam Uazman	23	5	Ziegler D	639
6	Feldman Eva L	20	6	Vinik AI	482
7	Emir Birol	17	7	Pop-busui R	476
8	Efron Nathan	16	8	Callaghan BC	390
9	Khan Adnan	15	9	Feldman EL	376
10	Boulton Andrew J M	15	10	Tavakoli M	331

Fig. 4 (A) Visualization network of author collaborations. (B) Top 20 authors' publications versus time. (C) Collaboration network of co-cited authors.



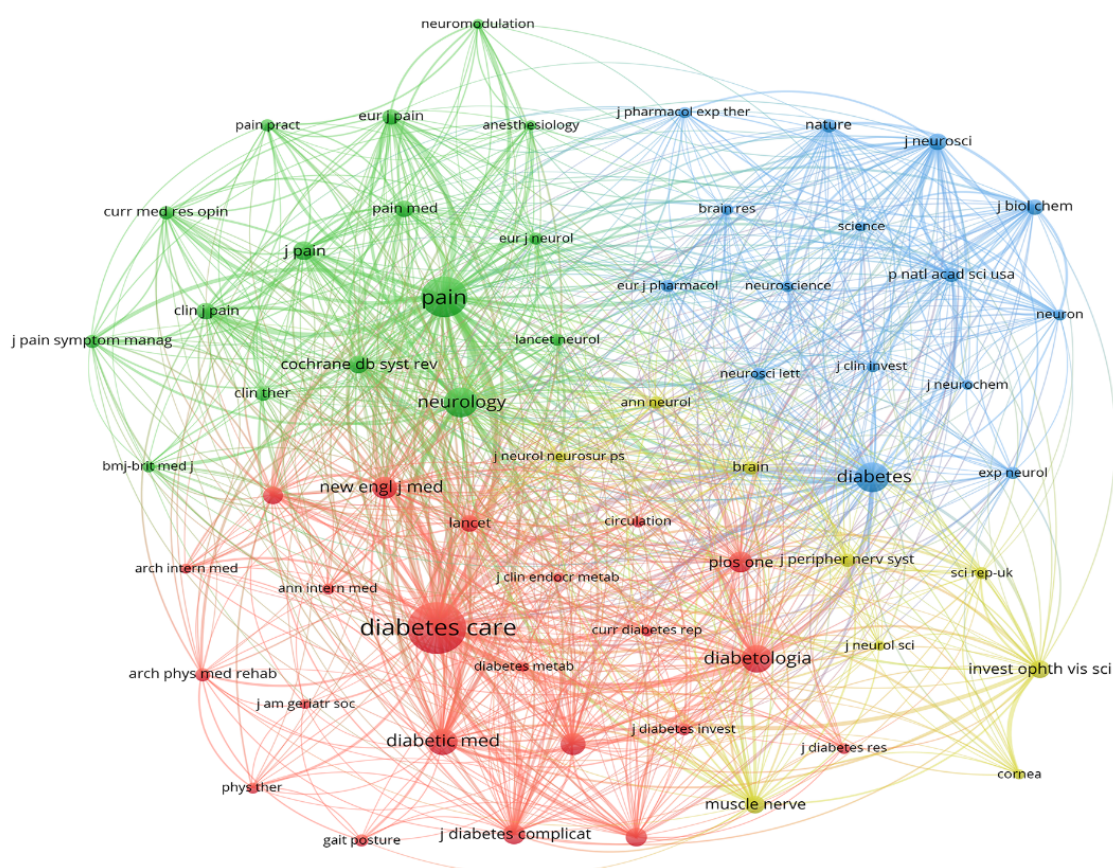
3.4 Co-cited journals

We screened 62 co-cited journals with ≥ 300 citations using VOSviewer to generate a co-occurrence network graph (Fig. 5), in which the top 10 co-cited journals all had >1000 citations (Table 4). Notably, compared to other journals, Diabetes Care had far more citations (8244 citations). Pain (4908 citations) and Neurology (2424 citations) came in second and third, respectively. Journals published in the United States and in the JCR Q1 partition dominated the top 10 rankings, with the New England Journal of Medicine having the highest Impact Factor (IF = 158.5). Four clusters were observed in which Pain, Diabetes and Diabetologia appeared to all have strong co-citation relationships with Diabetes Care (Fig. 5), demonstrating the importance placed on the reference value of high-quality journals in DPN research.

Table 4 Top 10 journals by number of co-citations.

Rank	Co-cite Journal	Records	Country	IF(2023)
1	Diabetes Care	8244	United States	Q1/16.2
2	Pain	4908	Netherlands	Q1/7.4
3	Neurology	2724	United States	Q1/9.9
4	Diabetes	2687	United States	Q1/7.7
5	Diabetologia	2392	Germany	Q1/8.2
6	Diabetic Medicine	2129	England	Q3/3.5
7	Diabetes Research Clinical Practice	1502	Netherlands	Q2/5.1
8	New England Journal of Medicine	1446	United States	Q1/158.5
9	Plos One	1380	United States	Q2/3.7
10	Journal of Diabetes and its Complications	1273	United States	Q3/3.0

Fig. 5 Diagrams of co-occurrence network of co-cited journals.



3.5 Co-cited references

We used VOSviewer to visualize and analyze the 106 references that were cited ≥ 50 times among the 71,054 references in the 2,761 DPN articles, generating a co-citation network graph of the references (Fig. 6A). The graph showed three notable clusters with the largest node having a maximum of 354 citations, followed by two articles published by Pop-Busui R and Boulton AJ, with 255 and 235 citations, respectively (Table 5), demonstrating the specific information of the top 10 DPN-related co-citations. Notably, the top three co-cited references were all reviews and published in Diabetes Care, correlating with Diabetes Care as the most cited journal. Furthermore, Prof. Tesfaye S from the UK was the most cited author, having published two of the top ten cited articles. The two articles were published in Diabetes Care (IF=16.2) and the New England Journal of Medicine (IF=158.5), showing the professor's significant contribution and influence in DPN research.

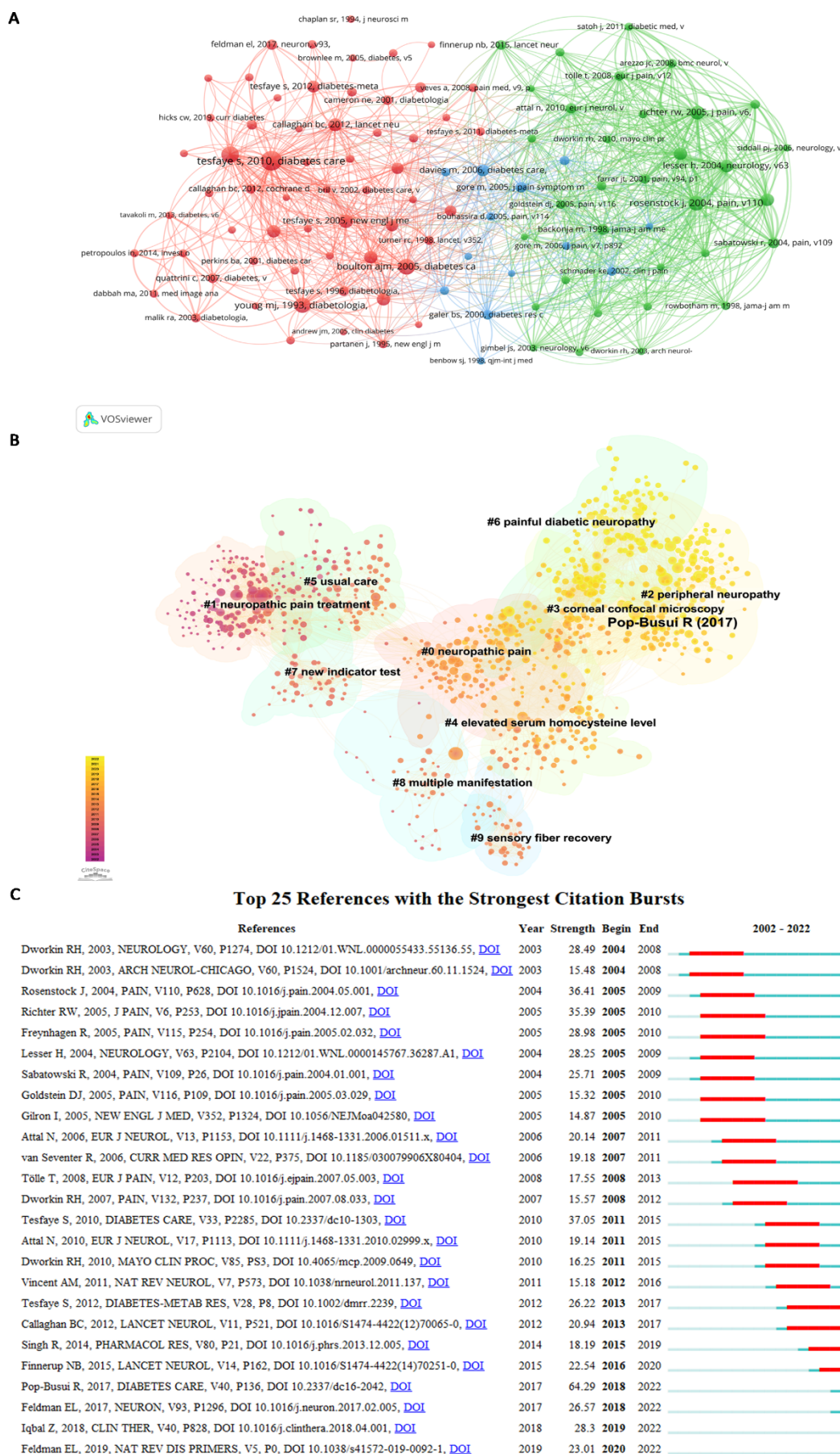
The keywords in the 71,054 references were clustered using the clustering function of the LLR algorithm in CiteSpace (Fig. 6B). The top 10 clusters included: #0 neuropathic pain; #1 neuropathic pain treatment; #2 peripheral neuropathy; #3 corneal confocal microscopy; #4 elevated serum homocysteine level; #5 usual care; #6 painful diabetic neuropathy; #7 new indicator test; #8 multiple manifestation; and #9 sensory fiber recovery (Fig. 6B). The top numbers had more articles in the cluster. Specifically, #0 neuropathic pain had the most articles, followed by #1 neuropathic pain treatment, and #6 painful diabetic neuropathy was the key element of the literature cited in recent years. The node in #6 had the warmest color, representing the cluster in which the articles were primarily from recent years, implying that the focus of DPN researchers has recently been revolving around addressing neuropathic pain symptoms. On the other hand, #3 corneal confocal microscopy represented an emerging hotspot in DPN research. The Confocal Microscope is currently considered one of the most valuable devices for clinically diagnosing and studying certain diseases.

We also analyzed the burst of cited references. Figure 6C shows the top 25 references based on the number of cited bursts, with each article having 4-5 years of citation bursts. Four articles in the field could still be in the strong citation phase. A statement on diabetic neuropathy published by Pop-Busui R and other members of the American Diabetes Association in Diabetes Care in 2017 had the strongest citation strength. This article reviewed the screening, diagnosis, and treatment of various diabetic neuropathies, including distal symmetric polyneuropathy, diabetic autonomic neuropathies, and atypical neuropathies^[18], respectively, offering researchers a useful theoretical reference.

Table 5 Top 10 references by number of co-citations.

Rank	Title	Article Type	Year	Total Citations	Author	Journal
1	Diabetic neuropathies: update on definitions, diagnostic criteria, estimation of severity, and treatments	Review	2010	354	Tesfaye S	Diabetes Care
2	Diabetic Neuropathy: A Position Statement by the American Diabetes Association	Review	2017	255	Pop-Busui R	Diabetes Care
3	Diabetic neuropathies: a statement by the American Diabetes Association	Review	2005	235	Boulton AJM	Diabetes Care
4	A multicentre study of the prevalence of diabetic peripheral neuropathy in the United Kingdom hospital clinic population	Article	1993	223	Young MJ	Diabetologia
5	Pregabalin for the treatment of painful diabetic peripheral neuropathy: a double-blind, placebo-controlled trial	Article	2004	199	Rosenstock J	Pain
6	Relief of painful diabetic peripheral neuropathy with pregabalin: a randomized, placebo-controlled trial	Article	2005	182	Richter RW	Pain
7	Vascular risk factors and diabetic neuropathy	Article	2005	177	Tesfaye S	New England Journal of Medicine
8	Diabetic neuropathy: clinical manifestations and current treatments	Review	2012	161	Callaghan BC	Lancet Neurology
9	Pregabalin relieves symptoms of painful diabetic neuropathy: a randomized controlled trial	Article	2004	154	Lesser H	Neurology
10	A practical two-step quantitative clinical and electrophysiological assessment for the diagnosis and staging of diabetic neuropathy	Article	1994	154	Feldman EL	Diabetes Care

Fig. 6 (A) Diagram of co-citation network of references. (B) Cluster diagram of co-cited references. (C) Top 25 References with the Strongest Citation Bursts.



3.6 Keywords analysis

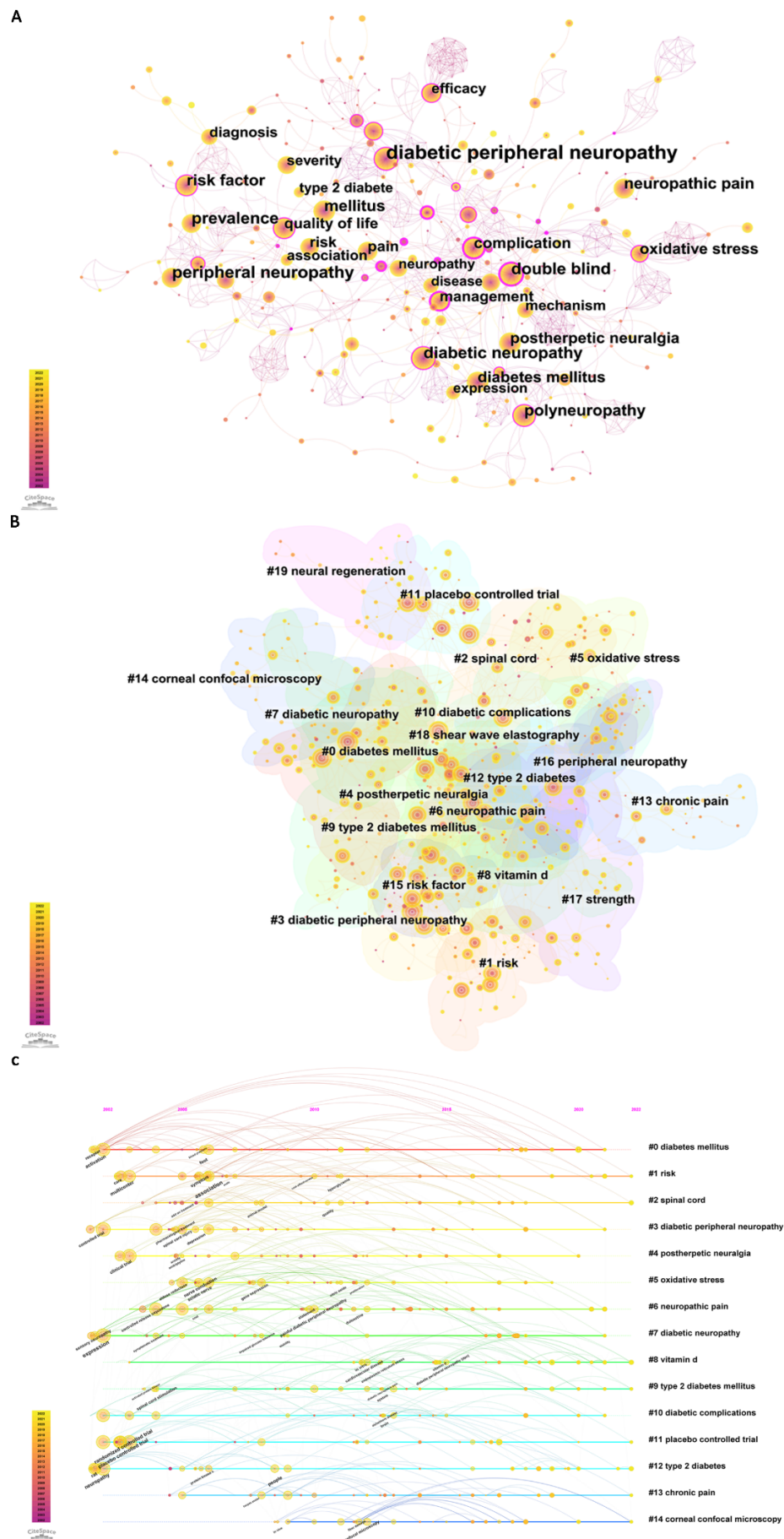
CiteSpace was used to visualize the keywords of the 2,761 DPN articles from different perspectives. Figure 7A shows the co-occurrence network of 456 keywords. Besides the keywords retrieved for this study, the other keywords with a high frequency of occurrence were peripheral neuropathy (n=422), diabetic neuropathy (n=342), double-blind (n=332), and prevalence (n=329). Among these keywords, double-blind had high centrality (Table 6), showing the importance of using double-blind experimental methods in DPN clinical research. Table 6 shows the top 20 keywords with the highest frequency and their centrality. Complication had the highest centrality, followed by management, implying the importance of studying various diabetic complications and their management.

The keyword information was further analyzed using cluster and timeline plots (Figs. 7B-C). We found that #11 placebo-controlled trial and #12 type 2 diabetes were the keywords with the longest duration, indicating that DPN research has been based on placebo-controlled trials and type 2 diabetes correlation with DPN. Besides #4 postherpetic neuralgia and #5 oxidative stress, the other categories with ongoing research included #1 risk, #2 spinal cord, #8 vitamin D, #13 chronic pain, and #14 corneal confocal microscopy. Furthermore, we analyzed the keyword burst phenomenon, and the top 25 keywords with the most citation bursts are shown in Supplementary Figure S1. Notably, foot ulceration and blood flow had the longest citation bursts, showing the importance of diabetic foot complications in DPN research before 2013. Postherpetic neuralgia, which also serves as a type of peripheral neuropathic pain had the highest citation intensity. Additionally, researchers were interested in the efficacy of various medications in treating postherpetic neuralgia and diabetic peripheral neuropathic pain. Gabapentin also had a high citation strength with a long burst period, implying that its underlying mechanism in treating DPN patients is a major research area. Systematic review, therapy, older adult, and adult are the four keywords from 2020 that are still in a strong citation burst period. This shows that DPN research has received more attention in multiple directions in recent years.

Table 6 The 20 keywords that appear most frequently in articles.

Rank	Keywords	Records	Centrality	Rank	Keywords	Records	Centrality
1	diabetic peripheral neuropathy	1193	0.1	11	postherpetic neuralgia	231	0.01
2	peripheral neuropathy	422	0	12	oxidative stress	229	0.16
3	diabetic neuropathy	342	0.12	13	diabetes mellitus	215	0
4	double blind	332	0.26	14	risk	195	0.04
5	prevalence	329	0.02	15	management	179	0.26
6	risk factor	265	0.11	16	pain	176	0.03
7	mellitus	261	0.05	17	quality of life	169	0.18
8	polyneuropathy	261	0.11	18	association	158	0.04
9	neuropathic pain	247	0	19	diagnosis	154	0.04
10	complication	237	0.36	20	severity	153	0.03

Fig. 7 (A) Diagram of co-occurrence network of keywords. (B) Network graph of the top 20 keyword clusters. (C) Timeline graph of keywords.



4. Discussion

Herein, we conducted a comprehensive and systematic bibliometric analysis of DPN articles published over the past 20 years. After a rigorous screening process, 2,761 articles from 99 countries/regions were obtained. We visualized and analyzed various aspects of the identified DPN articles, including yearly issuance, citation trends, countries/regions, institutions, authors, cited journals, references, and keywords to explore the changes in research trends and future research directions in the field of DPN. As a result, this study fills an existing knowledge gap in DPN and offers an essential reference for developing research on chronic diabetic complications.

4.1 General information

Publication of DPN articles has been largely on an upward trend since 2002 (Fig. 2). Specifically, the growth trend can be divided into two phases: 2002 to 2011, in which the rise in DPN research was relatively more sluggish, and the past ten years (2012-2022) in which the publication of DPN articles has increased significantly. The growth trend in the published DPN articles implies that DPN-related research is taking shape and will continue to be a developing and progressing field of study. Globally, the United States had the most DPN publications, followed by China, with both countries leading other nations/regions by a wide margin. Additionally, seven and six of the top 20 research organizations in terms of publications were from the United States and China, respectively. Notably, although both the United States and China had more publications than other countries, the United States had a significantly higher relative centrality than China, implying a higher quality and impact research from the United States. Prof. Malik Rayaz A of the University of Manchester, whose main research interests are DPN diagnosis and treatment, was the author with the most publications. On the other hand, Prof. Tesfaye S of British Sheffield Teaching Hospitals was the author with the most citations. Six of the top ten cited journals belonged to the JCR Q1 partition: Diabetes Care (IF=16.2); Pain (IF=7.4); Neurology (IF=9.9); Diabetes (IF=7.7); Diabetologia (IF=8.2); and the New England Journal of Medicine (IF=158.5).

4.2 Knowledge base

The 25 references with the strongest citation bursts were predominantly RCTs on pregabalin in treating postherpetic neuralgia conducted before 2010^[19-21] and painful DPN patients^[22-25]. These trials provide better evidence of the efficacy of pregabalin in treating neuropathic pain. In other drug efficacy studies, using an active placebo in the trial that differed from that used in previous studies, Gilron I et al.^[26] discovered that the combination of gabapentin and morphine had superior efficacy in treating neuropathic pain than either of the two medications alone in patients with painful diabetic neuropathy or postherpetic neuralgia. Moreover, their study offers a framework for future trials comparing drug combinations with individual drugs. In 2006, Attal N et al.^[27] (who are members of the European Federation of Neurological Societies) published the first guidelines for neuropathic pain treatment by examining clinical RCTs conducted over the past few years in various neuropathic pain conditions and comprehensively evaluating the efficacy and safety of the drugs, initially forming an expert consensus on the pharmacologic treatment of neuropathic pain, thereby bridging the gap in the field. This study offers clinicians an effective approach to treating neuropathic pain and multiple strategies for novel pharmacological trials for neuropathic pain treatment. In 2010, they revised and updated the guidelines to better define the response profile of medications for neuropathic pain and accommodate the needs of clinicians^[28]. Despite years of experimental clinical trials, there is still no cure for DPN. Therefore, far from the past focus on the efficacy of various medications in treating DPN symptomatic pain, researchers have begun to delve more deeply into the mechanisms underlying diabetic neuropathy development since 2010. Discoveries on DPN pathogenesis have been beneficial in addressing all its aspects, from prevention to treatment^[29]. In a comprehensive review of DPN cellular mechanisms published in Nature Reviews Neurology, Vincent AM et al.^[30] proposed cellular mechanisms as therapeutic targets for DPN treatment. This review delved into the activation of multiple cellular mechanisms in different diabetic settings, and presented new targets and strategies for diabetic neuropathy treatment, specifically cell protection, oxidation inhibition, and lowering of inflammatory responses, after analyzing the interactions between the different mechanisms as well as existing therapeutic strategies. In 2017, the University of Michigan's Feldman EL Professor^[31] and experts from the University of Oxford, Max Planck Institute for Experimental Medicine and Aarhus University authored a review proposing a new vision of diabetic neuropathy mechanisms. Their review details the structure of the Peripheral

Nervous System (PNS) and outlines the pathways leading to peripheral nerve damage in diabetic neuropathy. Furthermore, it discusses systems biology insights summarized from recent research breakthroughs in biotechnology and bioinformatics, presenting novel ideas focusing on the axon-schwann cell relationships and associated bioenergetics. The article adds new insights into the pathogenesis of diabetic neuropathy, facilitating the development of mechanism-based treatments. Notably, 15 of the 25 articles with the most cited outbreaks were reviews. This finding suggests that researchers value summarizing and evaluating major research directions in DPN. Moreover, the key insights discussed in these articles have drawn more scholars to the advances in DPN research, leading to the continuous development of DPN-related investigations.

4.3 Emerging topics

Scholars performing bibliometric analysis could use the frequency of keywords to determine important research directions in specific study fields. Herein, we identified “risk factor”, “corneal confocal microscopy”, and “systematic review” as the key hotspots through an in-depth analysis of the timeline graph of keyword clustering and the burst of keyword-related citation information. Existing diagnostic tests are difficult to perform, and there is also a lack of neurological damage treatments. Therefore, identifying risk factors for DPN, determining the early stage of disease onset, and consequently, early interventions, are critical in clinically controlling DPN progression. A retrospective cohort study revealed that age >66 years, history of hypertension, lymphocyte count, and HbA1c levels above a certain threshold were risk factors for DPN development in adult DM patients^[32]. Specifically, HbA1c change represented the long-term glycemic variability, which was evaluated using the HbA1c (Cv-HbA1c) coefficient of variation. Furthermore, increased HbA1c variability showed a greater correlation with DPN occurrence in Type 2 Diabetes Mellitus (T2DM) patients, as revealed by multivariate logistic regression and ROC analyses^[33]. Besides general information and blood glucose-related laboratory indices, there has also been an increasing exploration of other risk factors. For the first time, recent studies assessed the correlation between Fibrinogen/Albumin (FAR) and DPN. According to the results, FAR levels were higher in DPN patients than non-DPN patients and correlated negatively with nerve conduction velocity, indicating a better predictive value compared to fibrinogen^[34]. Melatonin levels, a key research focus in the pathogenesis of diabetes and its complications, have been demonstrated by melatonin gene polymorphisms to be associated with DPN^[35]. Ethnicity is significant in genetic studies, and the role of melatonin gene polymorphisms in other ethnicities as well as in larger groups of DM patients may be studied in the future. Metformin treatment is also being investigated as a risk factor for DPN development, with long-term metformin use being associated with increased DPN risk in older veterans^[36]. In Asian populations, DPN risk with metformin is more pronounced in younger patients and rises with the metformin dose used^[37]. Corneal Confocal Microscopy (CCM), an ophthalmic marker, is useful in DPN diagnosis^[38], and can noninvasively detect peripheral neuropathy and its severity in T2DM patients^[39] as well as predict DPN occurrence^[40]. Screening for DPN (using CCM) and retinopathy in diabetic patients in primary care has enabled the early detection of neuropathy in patients^[41]. Artificial Intelligence (AI) has been widely used in medical practice in recent years, and CCM’s AI-based deep learning algorithm can be used to differentiate DPN patients and non-DPN patients^[42], as well as healthy populations, DM patients without neuropathy, and DM patients with neuropathy, after development and improvement, using an image classification method^[43]. To maximize its benefits, CCM has also been sought to differentiate between diabetic neuropathy types, such as inflammatory and non-inflammatory neuropathies^[44]. Additionally, a previous systematic evaluation and meta-analysis demonstrated the diagnostic value of CCM in DPN patients^[45]. As one of the important sources of validation in evidence-based medicine, systematic evaluations are widely used in DPN research to address clinical issues. When critically evaluated and analyzed, the conclusions based on clinical DPN studies of various aspects inform clinical decision-making. Regarding disease risk factors, smoking, Tumor Necrosis Factor- α (TNF- α), and vitamin D have been evaluated for their correlation with DPN occurrence in DM patients^[46-48]. Regarding disease diagnosis, a systematic evaluation of available evidence revealed that the monofilament test could be insufficiently sensitive for screening DPN^[49], whereas clinical electrophysiologic examination provides the best quantitative indication for DPN^[50]. Regarding disease treatment, vitamin B12 supplementation with metformin therapy^[51], herbal footbaths in conjunction with acupuncture^[52], spinal cord stimulation along with conventional therapy^[53], and various exercise regimens^[54] have all been shown to be effective in DPN treatment. This approach is currently propelling additional high-quality clinical DPN research and better complements existing research guidelines.

5.Limitations

Despite providing a comprehensive bibliometric analysis of DPN articles using several visualization tools and demonstrating the DPN-related research hotspots and trends, this study still has some limitations. Literature search was restricted to the Web of Science Core Collection database and articles and reviews strictly in English, potentially excluding some valuable literature, thereby impacting the study conclusion. We will address these shortcomings in future research by expanding the literature sources.

Conclusion

To the best of our knowledge, this is the first study to visualize and analyze DPN articles. Specifically, it obtained general information on countries/regions, institutions, authors, and cited journals, as well as the trending research focus areas within the field of DPN in a cited literature burst, including the efficacy of various medications for treating symptomatic DPN pain and the mechanism underlying diabetic neuropathy development. Furthermore, based on DPN prevention, diagnosis, and treatment, we found that the main future DPN research directions revolve around actively searching for DPN risk factors, improving diagnostic capabilities using advanced technologies such as CCM, and providing more clinical evidence using systematic evaluation as a research methodology. Overall, we expect this study to be a valuable reference for experts and scholars in DPN research.

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Conflict of Interests

The authors declare that there is no conflict of interest regarding the publication of this paper.

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