An analysis and visualization of postherpetic neuralgia research between 1985 and 2022 using scientometrics

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Abstract

Background

This study aimed to highlight the status of research on PHN between 1985 and 2022 through a bibliometric analysis and a historical review.

Methods

The Web of Science database was searched, and 3,386 relevant articles were included in the study. Bibliometric analysis was used to review the field distribution, regional distribution, and research topic evolution.

Results

Trends identified in the literature indicate that research on PHN is increasing globally. The United States is the leading country, and the University of California system is the leading institution in terms of publications. Glaxosmithkline had the highest number of citation bursts, indicating its important role in PHN research and drug development. PHN is primarily associated with older age and immunosuppression. Treatment mainly involves pharmacological, nonpharmacological, and interventional treatments, although data supporting the use of physical interventions are lacking. The main psychophysiological effects experienced by patients with PHN are anxiety, insomnia, and depression. Additionally, PHN results in a significant economic burden. Two vaccines have been approved for herpes zoster. Finally, animal models of PHN are inadequate.

Conclusions

The findings of this study provide valuable information for future research on PHN, e.g., research is needed on the mechanism of PHN, the development of suitable animal models, and the long-term effects of interventional treatment.

1 Introduction

Postherpetic neuralgia (PHN) is the most frequent complication of herpes zoster (HZ). It is characterized by persistent pain after healing of herpetic skin lesions for more than 1 month or pain lasting at least 3 months after HZ onset. The symptoms of PHN include spontaneous throbbing, stabbing, shooting, or burning, usually accompanied by numerous abnormal sensory symptoms(Aggarwal et al., 2020). In addition, patients with PHN usually present with severe and prolonged psychophysiological problems, including sleep disturbances, anxiety, and depression[2].

PHN has long been the focus of research, and significant progress has been made in this regard[3, 4]. However, the mechanism of PHN remains largely unknown, and the incidence of refractory PHN remains high[5]. Research on PHN-related scientific issues must be continued and expanded. A systematic summary of global trends and hotspots is important for further studies.

Through statistical methods and visualizations, bibliometric analysis provides insights into the structure and trends of a given subject(Xu et al., 2021. At present, few bibliometric analyses have been conducted on PHN. In this study, we analyzed PHN research publications to identify high-impact countries, regions, institutions, authors, references, and journals. PHN hotspots and critical research fields were also investigated to understand the current status of PHN and propose future research directions.

2 Material and methods

2.1 Data collection

The data source for this bibliometric analysis was the Science Citation Index Expanded (SCI-E) in the Web of Science Core Collection. Documents were downloaded on November 21, 2022. The following keywords were used for publication retrieval: “postherpetic neuralgia” or “PHN” or “post herpetic neuralgia.” The search strategy also included publication year (1985 to November 21, 2022), language (English), and document type (article). For further analysis, the final records were downloaded in .txt format and imported into visualization and bibliometric tools. The journal impact factors (IFs) were derived from the journal citation report of Web of Science (WOS) (Clarivate, Philadelphia, PA), ranking of institutions was obtained from Scimago Institutions Rankings (https://www.scimagoir.com/rankings.php), and the H-index of countries/regions was retrieved from the Scimago Journal and Country Rank (https://www.scimagojr.com/journalrank.php). An individual’s H-index or global rank can be used to evaluate their academic performance and measure their achievements in science or their influence. The H-index indicates the largest number of papers (H) papers that have been cited at least H times.

2.2 Data analysis

Bibliometric analysis was conducted using CiteSpace (https://citespace.podia.com/), including the country, institution, author, keyword, category, reference, and journal. Time slicing (1985–2022), node types, and selection criteria (top 50 levels of most-cited or occurring items) were included in the parameter settings[6]. Node size indicates the number of articles. Publication years are represented by citation rings on the nodes. The line thickness indicates the frequency of cooperation among countries, regions, institutions, and authors. Keyword and author co-occurrences were visualized using VOSviewer software (version 1.6.18; https://www.vosviewer.com/). In the co-occurrence map, larger nodes imply a higher frequency co-occurrence of the item. A comprehensive analysis of the scientometric results was conducted using the IFs, global rankings, and H-indices. GraphPad Prism 8.4 software (GraphPad Software, San Diego, California USA; www.graphpad.com) was used to analyze the published data, productive countries, productive institutions, and hot categories. Figure 1 shows the workflow of the scientometric research(Xu et al., 2021).

3 Results and Discussion

3.1 Data overview and analysis

A total of 3,790 articles related to “postherpetic neuralgia” or “PHN” or “post herpetic neuralgia” were identified. After skimming the titles and abstracts of the articles in different journals, 404 articles unrelated to PHN were excluded. Finally, 3,386 articles were included in this study. Based on the search results in WOS, it can be seen that PHN was first proposed in 1997, with 64 publications annually. A rapidly increasing trend began in 2006 (n=124), and then the growth trend became relatively flat, with the largest number of papers published in 2017 (n=188) (Fig. 2). In addition, Pfizer contributed 17 papers in 2017, mainly because of its development of pregabalin[7,8]. The global trend suggests that PHN is receiving increasing attention as a typical form of neuropathic pain.

3.2 Countries/regions and institutions cooperation map

The collaboration network of the country/region and institution was obtained through CiteSpace. With 1,241 publications (36.694%), the United States (US) was the country with the most publications, followed by China, England,

Germany, Japan, Canada, Italy, South Korea, France, and Australia, with >100 articles each (57.89% of the total) (Fig. 3A–C). There has been close cooperation among countries in terms of research on PHN, highlighting its global nature. In developed countries, especially the US and European countries, the total number of articles is greater, which can be explained both objectively and subjectively. Objectively, scientific research is heavily funded in developed countries. Subjectively, greater focus has been placed on chronic pain in developed countries. Recently, PHN has gained increasing attention in China, with extensive research on neurobiological mechanisms, treatments, neuroimaging, and traditional Chinese medicine[8–10]. In terms of institutions, six US institutions ranked among the top 10. The University of California system ranks first among all institutions. In addition, three multinational corporations, Pfizer, GSK, and Merck, were listed among the top 10 as they contributed substantially to the development of PHN-related drugs and HZ vaccines(Parsons et al., n.d.; Garry et al., 2005; Curran et al., 2017). Another institution ranked in the top 10 was the University of London in the United Kingdom (UK) (n=62) (Fig. 3D, E).

A citation burst reflects a high rate of citation of a paper over a certain period. GSK had the highest number of citation bursts, indicating its important role in PHN research for its contribution to the mechanism of PHN, HZ vaccines, and PHN-related drugs(Jung et al., 2004; Chen et al., 2014; Cunningham et al., 2016). Additionally, GSK has conducted several high-quality clinical trials[17]. The University of California San Francisco, Merck Research Laboratories, and Harvard University also had high numbers of citation bursts. The US has several world-famous institutions and an H-index of 2711. Compared with other countries/regions, it has a distinct advantage and makes significant contributions to PHN research. Other prominent contributors to PHN research were England (1707), France (1352), Germany (1498), and China (1112) (Fig. 3C, E). It is worth noting that China has had a continued citation burst in recent years, suggesting its great potential in the field of PHN.

3.3 Analysis of authors

According to Citespace, Baron R was the most productive author, with 41 publications, primarily about clinical research on PHN[2,18], followed by DWORIN RH (n=30), JENSEN TS (n=27), LEVIN MJ (n=26), CURRAN D (n=24), ZHANG Y (n=23), and PARSONS B (n=23). BARON R, DWORIN RH, and JENSEN TS have continually contributed to this field since 1999. Many high-quality randomized controlled trials and systematic reviews have been performed[19,20]. LEVIN MJ has been using HZ vaccines since 2007[21]. ZHANG Y continually focused on the neuroimaging mechanism of PHN after 2014[22], and since 2018, CURRAN D has been studying the economic burden and impact of postherpetic neuralgia on quality of life[23]. DWORKIN RH had the highest number of citation bursts[24,25]. SCHMADER KE, VANHOVE GF, JENSEN TS, LEVIN MJ, and BARON R also had high numbers of citation bursts. The WOS data indicated that BARON R and DWORKIN RH, and BARON R and JENSEN TS cooperate (Fig. 4A, B).

3.4 Category analysis

The top 30 categories are shown in Figure 5. PHN is a typical neuropathic pain, with different mechanisms in the peripheral and central nervous systems involved in its pathogenesis[26]. Thus, 30.071% of the total publications were in the field of neuroscience and neurology. Medication is the cornerstone of PHN treatment, and a high number of papers on general internal medicine and pharmacology and pharmacy have been published (22.827% of total publications). Owing to the complexity of the mechanism, pharmacotherapy is not sufficient, and PHN is widely treated with interventions such as paravertebral nerve blocks, radiofrequency modulation, and spinal cord stimulation[27,28]. Anesthesiology (17.151% of total publications) had a higher number of publications than general internal medicine or pharmacology and pharmacy. As immunosuppression is believed to be the primary cause of HZ, a high number of publications were also found in immunology (6.18% of total publications). The role of microbiology in PHN has also

received significant attention (3.371%). Furthermore, psychological and psychiatric problems caused by long-term chronic pain in patients with PHN have also received attention (psychiatry accounts for 0.976% of total publications). In addition, our findings showed that PHN tended to occur in older populations and is often accompanied by kidney disease, surgery, rheumatism, and transplantation, indicating that PHN treatment should have broad and multifactorial considerations.

3.5 Journals and co-cited journals

Table 1 lists the top 30 journals for publications on PHN. *Pain* (n=156, 4.613%) ranked first, followed by the *Clinical Journal of Pain* (n=85, 2.513%) and *Pain Medicine* (n=69, 2.04%). Of the top 10 journals, six were from the US, two from the UK, one from New Zealand, and one from the Netherlands. In the top 30, there were 10 journals with IFs >5, including *Pain* (7.926), *Journal of Pain* (5.383), *Neurology* (11.8), *Journal of Pain and Symptom Management* (5.576), *Journal of Infectious Diseases* (7.759), *Anesthesiology* (8.986), *Anesthesia and Analgesia* (6.627), *Clinical Infectious Disease* (20.999), *Regional Anesthesia and Pain Medicine* (6.64), and the *Journal of Medical Virology* (7.85). The IF of *Pain Clinics* (0.165) was the lowest among the top 30 journals. As to the number of cited articles, *Pain* (n=1884) ranked first, followed by *Neurology* (n=1461), *New England Journal of Medicine* (n=1350), *Clinical Journal of Pain* (n=976), and *Journal of Pain* (n=857). Eight of the top 30 co-cited journals had IFs greater than 20, including the *New England Journal of Medicin*e (176.079), *Journal of the American Medical Association* (JAMA) (157.335), *Lancet Neurology* (59.935), *Clinical Infectious Diseases* (20.999), *Annals of Internal Medicine* (52.598), *British Medical Journal* (93.333), *Science* (63.714), and *Nature* (69.504). Meanwhile, six journals had IFs between 10 and 20: *Neurology* (12.258), *Mayo Clinic Proceedings* (11.104), *Proceedings of the National Academy of Sciences* (12.779), *Cochrane Database of Systematic Reviews* (12.008), *Brain* (15.255), and *Annals of Neurology* (11.274) (Table 2). Based on these results, we found that although the annual number of publications in this field is small, many high-quality studies are still being performed.

3.6 Co-cited references

The term “co-cited references” refers to references that have been cited by more than one article. In Table 3, the top 30 co-cited references related to PHN research are listed. Eight articles were co-cited over 1000 times, 14 articles were co-cited between 500 and 1000 times, and others were co-cited between 300 and 500 times. The top 30 co-cited papers were generally clinically relevant, including reviews, meta-analyses, clinical trials, epidemiological studies, guidelines, and pharmacological management studies (such as on pregabalin, opioids, and controlled-release oxycodone). Basic research is almost absent in the top 30, indicating that PHN-related basic research is still underexplored. However, PHN cannot be simulated in animal models because of the strict host specificity of the varicella zoster virus (VZV). By studying other mature neuropathic pain models, we may indirectly be able to uncover the mechanisms of PHN. Fourteen papers were published in top journals (IF >10): *Lancet* (n=1), *New England Journal of Medicine* (n=4), *JAMA* (n=2), *Lancet Neurology* (n=1), *Neurology* (n=4), and *Mayo Clinic Proceedings* (n=2). A timeline of the cited references is shown in Figure 6. The reference network map consists of 763 nodes and 3032 links. References were grouped into 12 clusters. Risk Factors (#4), Peripheral Neuropathy (#8), Painful Polyneuropathy (#9), and Oral Ketamine (#6) appeared first and ended in 2004. Active co-citations were found between the references in these clusters. The clusters Neuropathic Pain (#0) and Re-emerging Infection (#12) occurred later, followed by Painful HIV Neuropathy (#7), Prospective Study (#3), and Single-Center Randomized Controlled Trial (#13). Neuropathic Pain (#2) reappeared in 2001 and has continued ever since. The use of Health System (#1) and Abnormal Intrinsic Brain Activity (#5) appeared in 2007 and has continued in recent years. An active co-citation pattern exists among references, including for Neuropathic Pain and Abnormal Intrinsic Brain Activity clusters, suggesting that abnormal brain structure and function play a

significant role in neuropathic pain. Meanwhile, early treatment has been advocated in the majority of studies on neuropathic pain[29,30]. In addition, Neuropathic Pain appears twice, indicating that it has been the focus of research.

3.7 Co-occurrence analysis of keywords

Keyword analysis can provide an overview of hotspots and trends in the research field. As shown in Figure 7, 282 keywords with a frequency of more than five were identified. As shown in Figure 7A, PHN, HZ, and neuropathic pain were associated with larger nodes. These three keywords are closely connected and include six main aspects: risk factors, drug treatments, intervention treatment, pathogenesis, HZ vaccine research and development, and burden of disease. Neuropathic pain appeared first. HZ and PHN mainly appeared after 2012. Keywords such as pulsed radiofrequency (PRF), nerve block, electroacupuncture, dorsal root ganglion (DRG), functional magnetic resonance, vaccination, and burden of disease have appeared in recent years, indicating that these categories are hotspots. The results also indicated that basic research related to PHN is insufficient (Fig. 7B).

3.8 Keywords with citation bursts

Citation bursts not only indicate whether a field of research is active over a given period but also indicate emerging issues. According to keywords such as amitriptyline (strength, 28.0861; time span, 1997–2005), oral acyclovir (18.8104, 1997–2002), morphine (17.8331, 1997–2006), rat (15.1456, 1997–2008), ketamine (14.4117, 1997–2004), famciclovir (10.8216, 1997–2007), allodynia (10.5227, 1997–2007), acyclovir (10.0376, 1997–2004), PHN (9.417, 1997–2000) and receptor antagonist ketamine (8.275, 1997–2000), antiviral therapy and drug therapy were hotspots in the first decade, whereas morphine and ketamine were the most researched analgesics in the first few years[31–33]. Rat and allodynia persisted for the longest period, indicating that the animal model was the focus of PHN studies, and allodynia is the typical somatosensory phenotype of PHN[34–36] (Fig. 7C).

3.9 Major findings

To systematically understand PHN and inform future research directions, the top 15 keywords for each classification were summarized (Fig. 8).

3.9.1 Risk factors for PHN

PHN was primarily associated with older age and immunosuppression (Fig. 8A). The term immunosuppression applies to autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, solid organ transplantation, and chronic illnesses, including chronic kidney disease, chronic obstructive pulmonary disease, cancer, depression, diabetes mellitus, and hypertension.

Age was significantly associated with HZ. Although HZ can affect individuals of any age, the risk is increased in those older than 50 years[37]. It is estimated that the average annual incidence of HZ is 5.9–10 per 1000 person-years, which increases with age to 12 per 1000 in people older than 80 years(Schmidt-Ott et al., 2018; Buchan et al., 2021). Approximately 19.7% of patients with HZ develop PHN, increasing to 50% in patients over the age of 85 years[38]. Patients aged 40–49 years also experience an increase in incidence[39].

Cell-mediated immunity is crucial for keeping VZV dormant[21]. As reported, the incidence rate of PHN is 9.09% in immunocompetent patients. This rate increases to approximately 10.65–11.73% among immunocompromised

patients[17]. Bone marrow or stem cell transplants are linked to the highest incidence of HZ (43.33%), followed by solid organ transplantation, HIV infection, and systemic lupus erythematosus[40–44].

Numerous studies have implicated sex as a risk factor[45]. Women are more likely than men to suffer from PHN (5.33 per 1000 person-years compared with 4.61 per 1000 person-years)[46]. The presence of a prodrome, severe skin lesions, and a more severe rash are also risk factors for PHN[47]. Sleep shortages may be a new risk factor for PHN[47].

3.9.2 Pathogenesis of PHN

The mechanisms underlying the induction and maintenance of PHN are not fully understood. Several sites have been implicated in the development of PHN, including the endings of peripheral sensory neurons, DRGs, the spinal dorsal horn, and the brain[10,48]. Different mechanisms have been suggested to be involved in the development of PHN[34] (Fig. 8B).

There is abundant evidence that peripheral and central sodium ion channels play an important role in neuropathic pain[49,50]. In the painful skin of patients with PHN, the expression of Nav1.8 in keratinocytes was increased(Zhao et al., 2008). In DRGs, increased expression of Nav1.3 and Nav1.8 sodium channels could also be induced by VZV infection[13]. The ARTX-PHN-like model induced Nav1.7 upregulation in DRGs by increasing extracellular signal-regulated kinase phosphorylation[51].[52]

Voltage-gated calcium channels are also the primary mechanisms involved in PHN[45]. Cav3.2 expression in the DRG and spinal dorsal horn was significantly upregulated by VZV infection. The α2δ1 subunit of the voltage-gated Ca2+ channel bound to the presynaptic N-methyl-D-aspartate (NMDA) receptor in the spinal cord might contribute to tactile allodynia in PHN[38,40].

During VZV infection, immune cells play a crucial role in the regulation of HZ and PHN pathogenesis[53]. VZV infection triggers T cell-mediated immunity, and VZV-specific T cells infiltrate the ganglia and release tumor necrosis factor-α. This causes pain(Peng et al., 2022). Immune–glia interactions in the sensory ganglia play a critical role in herpetic neuralgia[54].

It has been well documented that NMDA receptors (NMDARs) play an important role in the development and maintenance of neuropathic pain states[55,56]. NMDAR activity and phosphorylation are critical for synaptic plasticity and central sensitization in neuropathic pain[57]. Blocking NMDARs may reduce central sensitization induced by nerve injury, resulting in long-lasting antiallodynia[58]. Other factors such as inflammation and oxidative stress are also involved in PHN. A pro-inflammatory protein expressed in the DRGs, S100 calcium-binding protein A9 (S100A9), plays a crucial role in the development of PHN[59]. Potassium channel deregulation and suppression of brain-derived neurotrophic factor also play a role in the pathogenesis of PHN[60,61].

The study of postherpetic pain using functional magnetic resonance imaging has enhanced our understanding of its neurophysiological mechanisms[62]. Anatomic/microstructural and functional abnormalities in the pain matrix, brainstem, and limbic system are associated with PHN[60]. A dynamic shift was observed in brain functional connection alterations in the rat model of PHN, shifting from sensory information to emotions and motivations[26,61].

3.9.3 Treatment

Treatment for PHN focuses primarily on relieving pain and improving quality of life. There are several types of treatments for neuropathic pain, including pharmacological, nonpharmacological, and interventional treatments[63].

4.9.3.1 Pharmacological therapies

For the treatment of PHN, tricyclic antidepressants (amitriptyline), gabapentin, pregabalin, and lidocaine 5% patches are commonly used[64]. Among the second-line treatments, strong or weak opioids (tramadol, oxycodone) are available, as well as selective serotonin/norepinephrine reuptake inhibitors (duloxetine, venlafaxine) and topical capsaicin cream or 8% capsaicin gel (Fig. 8C)[65].

Pregabalin, an antiepileptic drug targeting the calcium channel α2δ subunit, includes sustained-release pregabalin and immediate-release pregabalin. It can improve pain and sleep in patients and is well-tolerated in Chinese patients[8,66]. In contrast to pregabalin, mirogabalin is a novel selective oral α2δ ligand with higher binding affinities in human and rat α2δ subunits and dissociates more slowly from the α2δ1 subunit than the α2δ2 subunit. It appears that mirogabalin may be an alternative therapeutic option for treating PHN, as it is well-tolerated[67,68]. Gabapentin immediate release formulation and gabapentin gastric retention formulation have been approved for the treatment of PHN[69,70].

Sodium-conducting voltage-gated sodium channels are blocked by lidocaine 5% patches, which reduces ectopic impulses from primary afferent nerves after injury[71]. It is easy to use, well tolerated, has low systemic exposure, and thus, has a low risk of pharmacological interactions[72]. In patients with PHN, it relieves pain and reduces the severity of allodynia[73]. Lidocaine medicated plasters are cost-effective treatments in the Chinese medical insurance system and can reduce the economic burden on patients with PHN[74]. Numerous studies have shown that intravenous lidocaine infusion reduces analgesic consumption and improves the emotional and health status of patients with PHN[75].

The capsaicin 8% patch was found to provide effective and sustained pain relief in a European population with PHN[76]. A single 60-minute application of an 8% capsaicin dermal patch could significantly reduce PHN, with a sustained effect over a 12-week period[77].

Opioids effectively treat PHN without impairing cognition[33]. In patients with relatively higher baseline heat–pain thresholds, there was a greater reduction in pain and a higher rating of pain relief[78].

Vitamin C has been suggested to enhance the analgesic effects of gabapentin[79]. The administration of vitamin C can relieve spontaneous pain in patients with PHN[80]. Cannabinoid compounds may also represent a therapeutic avenue for the treatment of PHN[81].

4.9.3.2 Intervention treatment

Many studies have shown that interventional procedures are safe and effective alternatives to pharmacological treatments owing to fewer side effects. PRF, peripheral nerve stimulation, neuromodulation, spinal cord stimulation, and nerve block are common interventional treatments (Fig. 8D)[82].

Through the inhibition of Nav 1.7 upregulation, PRF therapy could significantly reduce pain in patients with PHN[51]. Thus, high-voltage, long-duration bipolar PRF may be a safe and effective therapeutic option(Wan et al., 2016). Compared with PRF, spinal cord stimulation could provide a better and longer-lasting analgesic effect[28,83]. Fire needles and acupuncture have also been suggested for PHN treatment[84].

However, data supporting the use of physical interventions in PHN are lacking, and long-term benefits have not been consistently observed.

4.9.4 Individual and social effects

Patients with PHN experience considerable anxiety, insomnia, and depression, which negatively affect their quality of life. It was reported that 69.0% of patients with PHN experience depression, and 65.8% experience anxiety (Du et al.,

2021). Furthermore, PHN can affect social functioning, engagement, and the ability to work, putting a significant economic burden on families and society (Fig. 8E).

In Europe, the mean per case direct cost of treating PHN is approximately EUR 406.04 to EUR 485.51[85]. PHN treatment costs in Ireland range from EUR 140 to EUR 313 per case, and the annual direct costs of treating PHN totaled EUR 179,277 (range: EUR 143,422 to EUR 215,132)[86]. In Italy, the cost per case of PHN is EUR 5,400[71]. Furthermore, the UK estimates that direct treatment of PHN costs approximately GBP 340 per episode[87].

In Canada, the total annual cost of PHN was over CAD 565,449 from 1997 to 2012[39]. PHN costs USD 2,000 in Latin America for those aged 50 years and older: USD 773 in indirect costs, and USD 1,227 in direct costs[88]. Annual excess health care costs attributed to PHN ranged from USD 1400 to USD 4,000 in the US[89].

In Singapore, the cost of treating one patient with PHN is approximately SGD 414.69[90]. The disease burden of PHN in China remains low. Based on the findings of Xiaohui *et al.*, outpatient care and inpatient care costs were CNY 560.2 and CNY 8116.9, respectively, for initial HZ episodes[91].

4.9.5 Prevention

The US Food and Drug Administration has approved two vaccines for the prevention of HZ and PHN: the live-attenuated zoster vaccine live (ZVL) and the recombinant zoster vaccine (RZV)[92]. Compared with ZVL, RZV may avert more PHN and is safer[93].

HZ is reduced by VZV vaccines, making them effective in preventing PHN[21,94,95]. There is evidence that HZ vaccines may reduce PHN incidence by up to 66.5%[96]. Statistically significant vaccine efficacy persisted for up to 8 years after vaccination(Morrison et al., 2015). Based on vaccine price, it is the most cost-effective to recommend vaccine for individuals aged ≥60 years with no contraindications[97]. In addition, the HZ vaccine could significantly reduce the incidence of HZ in people aged 50–59 years[98].

Two-dose vaccination against PHN is effective in 76.0% of cases, and second doses administered beyond the recommended 6 months do not negatively affect effectiveness[99]. In patients with HZ, despite previous vaccination, the incidence of PHN was low in women but not in men[100].

In addition, antiviral agents can prevent PHN if taken within 72 h of HZ onset. One study suggested that the incidence of PHN in patients treated with antivirals during acute HZ was lower than in untreated patients (2.6% *vs.* 18.6%)[101]. Regarding first-line antiviral therapy, famciclovir was prescribed most frequently (37%), followed by valaciclovir (36%) and acyclovir (19%). When compared with traditional 7-day antiviral therapy, a 14-day course of famciclovir can reduce PHN in elderly patients with HZ[102].

Early treatment of pain with pregabalin or gabapentin may be effective in reducing the risk of PHN[103,104].

4.9.6 Animal models of PHN

It is not possible to fully replicate the clinical manifestation of PHN in animal models because VZV is highly host specific. In recent years, PHN mechanisms have been studied using three animal models.

Takasaki *et al.* first inoculated mice with herpes simplex virus 1 (HSV-1) to induce HZ-like skin lesions, herpetic and postherpetic pain, and transient allodynia (no more than 7 days). However, hypesthesia and hypoalgesia were not observed in these animals(Takasaki et al., 2000). In addition, HSV-1 resulted in central nervous system infection in up to 20% of animals.

Another model of HZ-associated pain was constructed by inoculating mouse footpads with VZV. Mechanical allodynia and thermal hyperalgesia were induced and lasted for at least 3–4 days post-infection up to 60 days post-infection. Thus, this study provides a robust platform for investigating the pathogenesis of VZV-induced allodynia. However, in this model, HZ-like skin lesions were not observed, and replicating viruses were not detected[35,52].

Third, a non-viral PHN model, named the RTX-PHN-like model, was established by injecting resiniferatoxin (RTX) intraperitoneally into adult rats; in this model, thermal sensitivity was decreased, and tactile sensitivity was increased[10].

4 Future research direction

Multiple pathological mechanisms are involved in PHN development. Although great progress has been made, the specific mechanism of PHN remains unclear, and the therapeutic effect of current treatments is unsatisfactory. Moreover, animal models still need improvement, and an orofacial animal model for PHN is still lacking. Although interventional therapies are widely used for the treatment of PHN, large-sample, high-quality clinical studies are needed as different studies have reported inconsistent results regarding the long-term treatment effects of interventional treatment. Therefore, research on the mechanism of PHN and multi-center, large-sample, high-quality clinical studies on intervention therapy should be the focus of future research.

5 Limitations

The present study has some limitations. First, it was not possible to avoid false conclusions in this study because the bibliometric software is unable to distinguish between authors with the same initials. Second, the search terms used in this study inevitably included a small number of irrelevant studies while ensuring the recall ratio.

6 Conclusion

An SCI-E database search was performed using scientometrics. For research on PHN, the most productive country, institution, author, category, journal, and most cited journal, article, and keywords were analyzed. Through co-occurrence analysis of keywords, the clinical and basic research status of PHN was summarized, including risk factors, pathogenesis, therapy, individual and social effects, prevention, and animal models. Our results highlight the current research hotspots and reveal key research directions for further research. Overall, as a global disease, research on PHN among different countries, institutions, and authors is closely connected. However, research into the mechanism of PHN and high-quality clinical research is still insufficient, and this gap should be addressed in future studies.

Abbreviations

PHN: Postherpetic neuralgia, HZ: herpes zoster, IFs: impact factors, WOS: Web of Science, US: United States, UK: United Kingdom, DRG: dorsal root ganglia, PRF: pulsed radiofrequency, VZV: varicella zoster virus, SCI-E: Science Citation Index Expanded, NMDA: N-methyl-D-aspartate, HSV-1: herpes simplex virus 1, ZVL: zoster vaccine live, RZV: recombinant zoster vaccine

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

Xueqin Cao: Data curation, Formal analysis, Visualization, Writing–Original draft, Writing–review&editing. Mi Zhang: Formal analysis, Visualization, Writing–Original draft, Writing–review&editing. Caixia Zhang: Data curation, Formal analysis, Writing - review&editing. Bo Jiao: Data curation, Validation, Writing - review&editing. Hua Zheng: Validation, Writing–review&editing. Xianwei Zhang: Conceptualization, Visualization, Formal analysis, Writing–review&editing.

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Tables

Table 1. The top 30 journals related to postherpetic neuralgia research

Rank	Number of Publication	% of Total Publication	Journal			
			Name	Country/Region	Impact Factor (2022)	H-Index (2022)
1	156	4.613	PAIN	United States	7.926	269
2	85	2.513	CLINICAL JOURNAL OF PAIN	United States	3.423	130
3	69	2.04	PAIN MEDICINE	United Kingdom	3.637	103
4	54	1.579	JOURNAL OF PAIN RESEARCH	New Zealand	2.832	55
5	53	1.567	PAIN PHYSICIAN	United States	4.396	104
6	53	1.567	JOURNAL OF PAIN	United States	5.383	136
7	46	1.36	VACCINE	Netherlands	4.169	191
8	43	1.271	EUROPEAN JOURNAL OF PAIN	United States	3.651	114
9	41	1.212	PAIN PRACTICE	United Kingdom	3.079	64
10	35	1.035	PLOS ONE	United States	3.752	367
11	35	1.035	NEUROLOGY	United States	12.258	378
12	32	0.946	HUMAN VACCINES IMMUNOTHERAPEUTICS	United States	4.526	69
13	30	0.887	BMC INFECTIOUS DISEASES	United Kingdom	3.667	112
14	30	0.887	JOURNAL OF PAIN AND SYMPTOM MANAGEMENT	United States	5.576	147
15	29	0.857	JOURNAL OF INFECTIOUS DISEASES	United Kingdom	7.759	261
16	28	0.828	MEDICINE	United States	1.817	155
17	27	0.798	CURRENT MEDICAL RESEARCH AND OPINION	United Kingdom	2.705	111
18	27	0.798	ANESTHESIOLOGY	United States	8.986	245
19	26	0.769	CLINICAL THERAPEUTICS	United States	3.637	140
20	25	0.739	NEUROMODULATION	United Kingdom	3.025	64
21	25	0.739	ANESTHESIA AND ANALGESIA	United States	6.627	208
22	23	0 68	CLINICAL INFECTIOUS DISEASES	United States	20.999	353
23	21	0.621	PAIN RESEARCH MANAGEMENT	Canada	2.667	60
24	20	0.59	PAIN CLINIC	United Kingdom	0.165	20
25	19	0.562	BRAIN RESEARCH	Netherlands	3.61	212

26	19	0.562	RAGIONAL ANESTHESIA AND PAIN MEDICNE	United States	6.64	114
27	15	0.444	JOURNAL OF DERMATOLOGY	United States	3.726	70
28	15	0.444	JOURNAL OF MEDICAL VIROLOGY	United States	7.85	137
29	14	0.414	CLINICAL DRUG INVESTIGATION	United Kingdom	3.58	60
30	14	0.414	EUROPEAN JOURNAL OF PHARMACOLOGY	Netherlands	5.195	189

Table 2. The top 30 co-cited journals related to postherpetic neuralgia research.

Rank	Cite Number	Journal			
		Name	Country/Region	Impact Factor (2022)	H-Index (2022)
1	1884	PAIN	United States	7.926	269
2	1461	NEUROLOGY	United States	11.8	378
3	1350	NEW ENGLAND JOURNAL OF MEDICINE	United States	176.079	1079
4	976	CLIBICAL JOURNAL OF PAIN	United States	3.423	130
5	857	JOURNAL OF PAIN	United States	5.383	136
6	797	JAMA-JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION	United States	157.335	709
7	736	LANCET NEUROLOGY	United Kingdom	59.935	351
8	632	CLINICAL INFECTIOUS DISEASES	United States	20.999	353
9	604	JOURNAL OF PAIN AND SYMPTOM MANAGEMENT	United States	5.576	147
10	585	JOURNAL OF INFECTIOUS DISEASES	United Kingdom	7.759	261
11	534	ANESTHESIOLOGY	United States	8.986	245
12	524	EUROPEAN JOURNAL OF PAIN	United States	3.651	114
13	522	PAIN MEDICINE	United Kingdom	3.637	103
14	511	ANESTHESIA AND ANALGESIA	United States	6.627	208
15	487	MAYO CLINIC PROCEEDINGS	United Kingdom	11.104	191
16	468	ANNALS OF INTERNAL MEDICINE	United States	51.598	403
17	444	ARCH INTERN MED	Poland	5.218	39
18	438	P NATL ACAD SCI	United States	12.779	805
19	434	VACCINE	Netherlands	4.169	191
20	427	JOURNAL OF NEUROSCIENCE	United States	6.709	171
21	411	BRIT MED J	United Kingdom	93.333	392
22	407	ANN NEUROL	United States	11.274	308
23	364	SCIENCE	United States	63.714	1229
24	348	COCHRANE DB SYST REV	United Kingdom	12.008	292
25	345	NEUROSCIENCE LETTER			
26	334	BRAIN	United	15.255	351

			Kingdom		
27	325	NATURE	United Kingdom	69.504	1276
28	324	PLOS ONE	United States	3.752	367
29	321	BRAIN RESEARCH	Netherlands	3.676	212
30	313	PAIN PRACT	United Kingdom	3.079	64

Table 3. The top 30 cited articles related to postherpetic neuralgia research.

Rank	Cite Number	The Title of Article	Journal				
			Year	Name	Country /Region	Impact Factor (2022)	H-Index (2022)
1	3494	Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale	2001	Pain	United States	7.926	269
2	1667	Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis	2015	Lancet neurology	United Kingdom	59.935	351
3	1582	Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): Standardized protocol and reference values	2006	Pain	United States	7.926	269
4	1551	A vaccine to prevent herpes zoster and postherpetic neuralgia in older adult	2005	NEJM	United States	176.079	1079
5	1549	Neuropathic pain: aetiology, symptoms, mechanisms, and management	1999	LANCET	United Kingdom	202.731	807
6	1425	Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4)	2005	Pain	United States	7.926	269
7	1157	EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision	2010	European Journal of Neurology	United Kingdom	6.288	130
8	1028	Gabapentin for the treatment of postherpetic neuralgia - A randomized controlled trial	1998	JAMA-Journal of the American Medical Association	United States	157.335	709
9	902	Quantitative sensory testing: a comprehensive protocol for clinical trials	2006	European Journal of Pain	United States	3.651	114
10	856	Opioids in chronic non-cancer pain: systematic review of efficacy and safety	2004	Pain	United States	7.926	269
11	853	Recommendations for the Pharmacological Management of Neuropathic Pain: An Overview and Literature Update	2010	Mayo Clinic Proceedings	United Kingdom	11.104	191
12	846	The Erector Spinae Plane	2016	Regional	United States	5.564	114

		Block A Novel Analgesic Technique in Thoracic Neuropathic Pain		Anesthesia and Pain Medicine			
13	804	Herpes zoster	2002	NEJM	United States	176.079	1079
14	706	Morphine, gabapentin, or their combination for neuropathic pain	2005	NEJM	United States	176.079	1079
15	604	Pathobiology of neuropathic pain	2001	European journal of pharmacology	NERTHELANDS	5.195	189
16	685	The evidence for pharmacological treatment of neuropathic pain	2010	Pain	United States	7.926	269
17	656	Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): Somatosensory abnormalities in 1236 patients with different neuropathic pain syndromes	2010	Pain	United States	7.926	269
18	644	The epidemiology of chronic pain of predominantly neuropathic origin. Results from a general population survey	2006	Journal of Pain	United States	5.383	136
19	549	Pregabalin for the treatment of postherpetic neuralgia - A randomized, placebo-controlled trial	2003	Neurology	United Kingdom	11.8	315
20	535	A population-based study of the incidence and complication rates of herpes zoster before zoster vaccine introduction	2007	Mayo Clinic Proceedings	United Kingdom	11.104	191
21	521	Development and preliminary validation of a pain measure specific to neuropathic pain: The neuropathic pain scale	1997	Neurology	United Kingdom	12.258	315
22	520	The incidence and lifetime prevalence of neurological disorders in a prospective community-based study in the UK	2000	Brain	United Kingdom	15.255	351
23	496	Treatment of Neuropathic Pain: An Overview of Recent Guidelines	2009	American Journal of Medicine	United States	5.928	237
24	496	Pregabalin for the treatment of painful diabetic peripheral neuropathy: a double-blind, placebo-controlled trial	2004	PAIN	United States	7.926	269
25	483	Efficacy of the Herpes Zoster Subunit Vaccine in Adults 70 Years of Age or Older	2016	NEJM	United States	176.079	1079

26	438	Efficacy of oxycodone in neuropathic pain - A randomized trial in postherpetic neuralgia	1996	Neurology	United Kingdom	12.258	315
27	436	Gabapentin in postherpetic neuralgia: a randomised, double blind, placebo controlled study	2001	Pain	United States	7.926	269
28	435	Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis	2005	Neurology	United Kingdom	11.8	315
29	399	External validation of IASP diagnostic criteria for complex regional pain syndrome and proposed research diagnostic criteria	1999	Pain	United States	7.926	269
30	396	Risk of Herpes Zoster in Patients With Rheumatoid Arthritis Treated With Anti-TNF-alpha Agents	2009	JAMA	United States	157.335	709

Figures

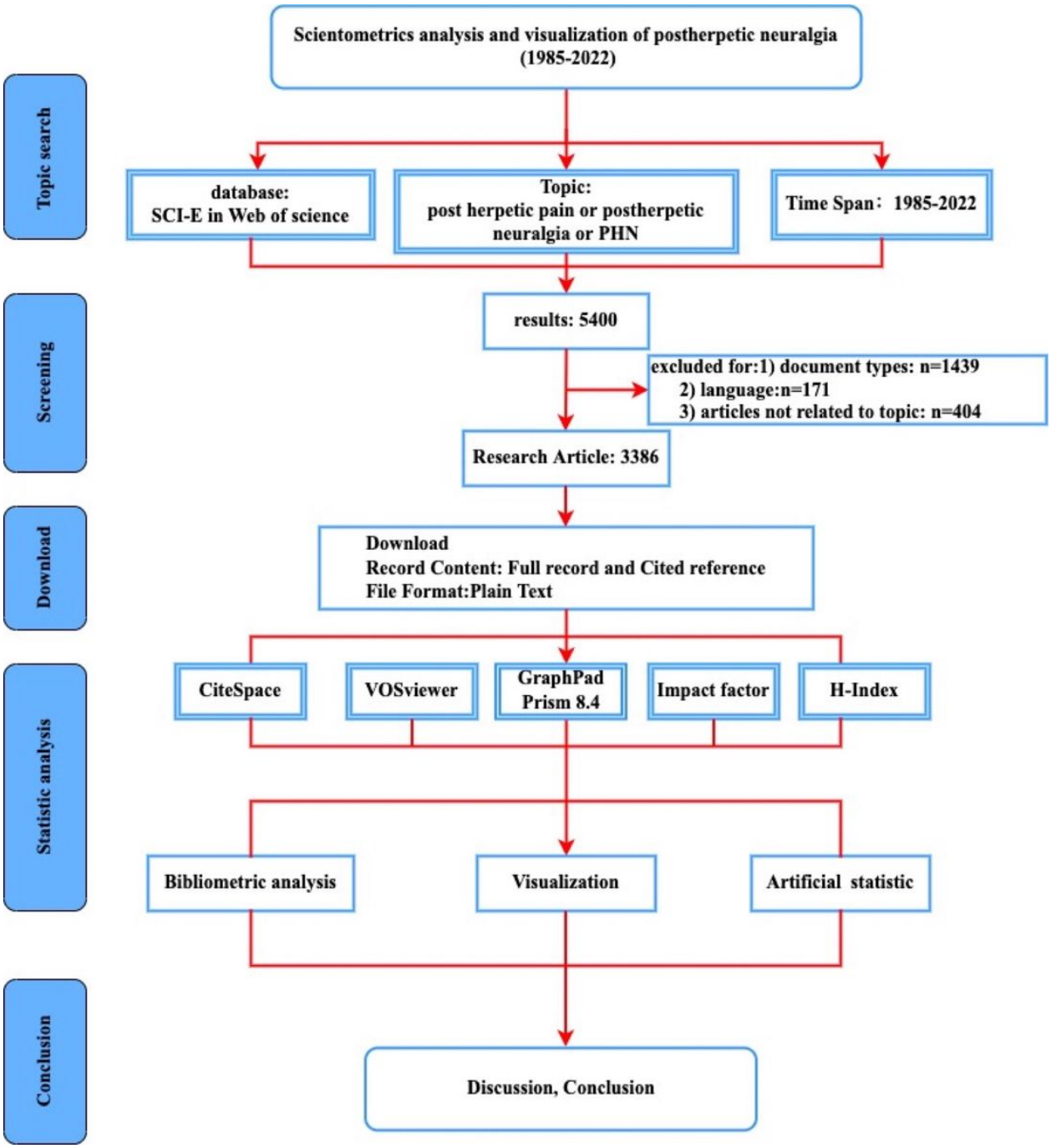

Figure 1

Flow chart of scientometric analysis. SCI-E = Science citation index expand; IF = impact factor; H-index = high citation index

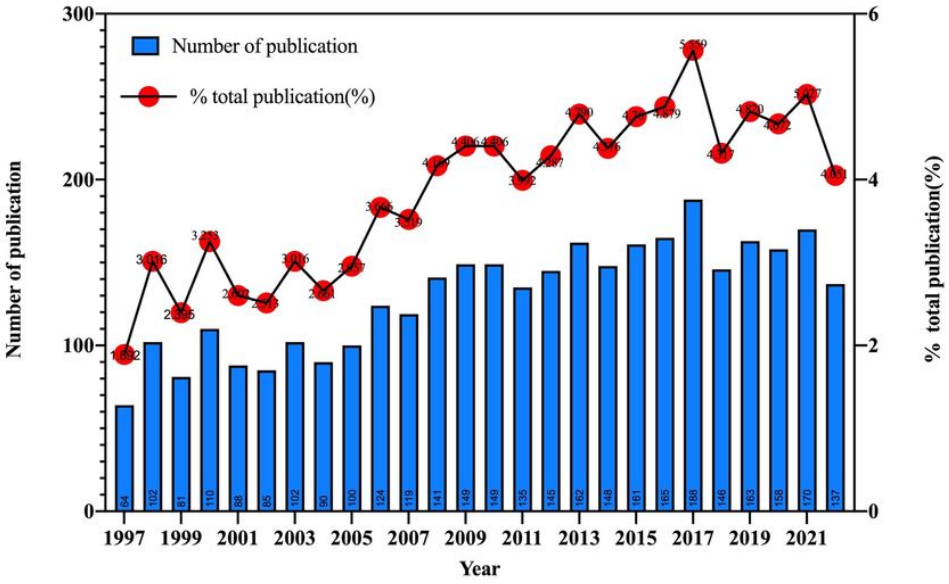

Figure 2

The number of annual publications.

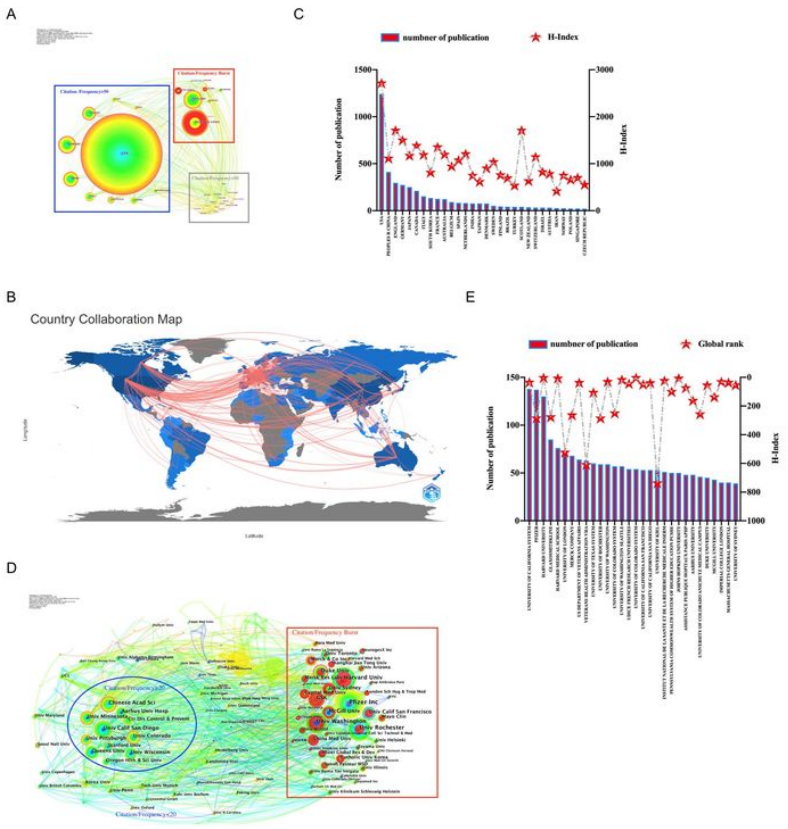

Figure 3

Cooperation map of country/region and institute. A) Country/region cooperation network. 52 nodes and 367 connection lines emerged. Node and line size represent the number of publications from a country/region and the cooperative relationship in the country/region, respectively. Red nodes indicate that publications of the country/region have citation or frequency burst. Connecting lines of different colors represent different years. Blue rectangle shows a citation/frequency of ≥50 for a country/region. Gray rectangle indicates citation/frequency of <50 for a country/region. Red rectangle indicates a burst in the citation/frequency of country/region. B) World map of the distribution of countries/regions in this field. C) Number of publications and H-Index scores for countries/regions. D)Institute cooperation network. 515 nodes and 1323 connection lines emerged. Node size and lines represent the number of publications from institutes and their cooperative relationship, respectively. Red nodes indicate a citation/frequency burst in publications of the institutes. Connecting lines of different color represent different years. Blue ellipse shows

that the citation/frequency of institute is ≥20. The outside of the blue ellipses indicates that the citation/frequency of the institute is <20. Red rectangles indicate citation/frequency burst of the institute. E) Number of publications and global institutional rank.

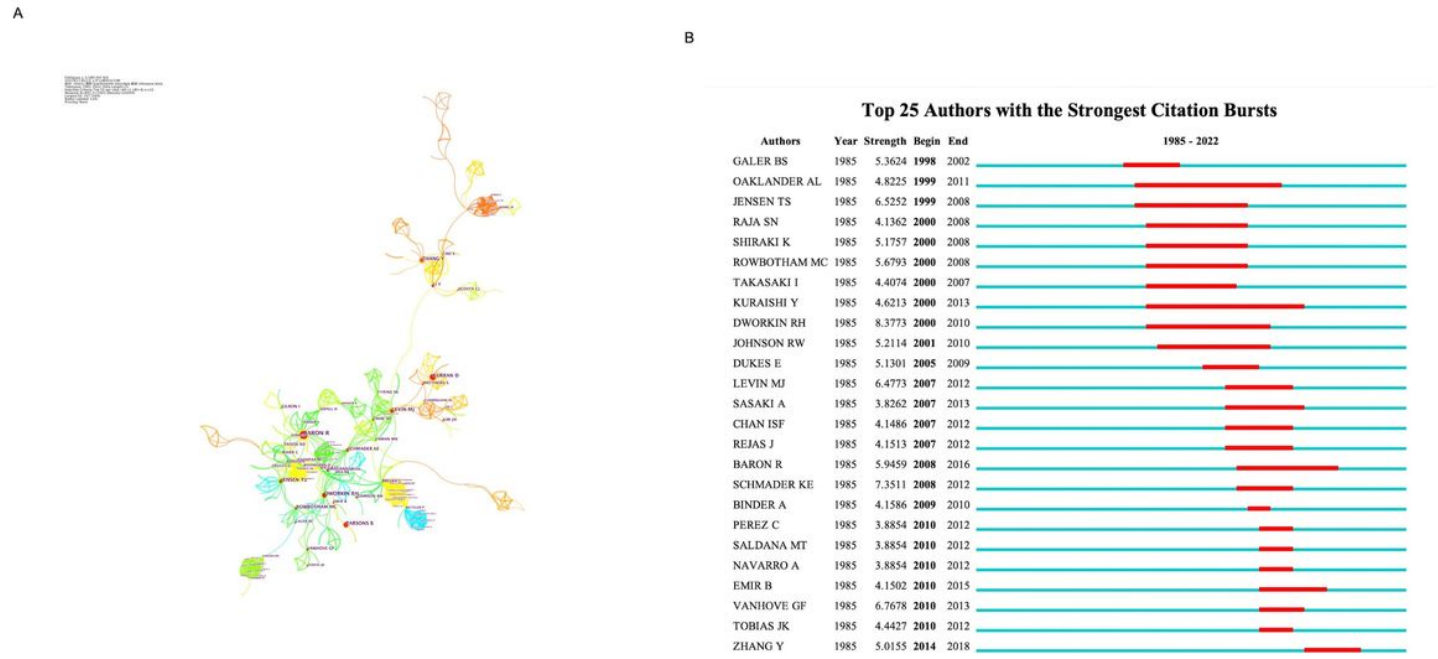

Figure 4

Cooperation map of authors. A) Author cooperation network. 891 nodes and 1943 connection lines emerged. Node and line size represent the number of publications from an author and the cooperative relationship in the different authors, respectively. Red nodes indicate that publications of the author have citation or frequency burst. Connecting lines of different colors represent different years. B) Top 25 authors with strongest citation bursts. Red bars mean that some authors are cited frequently in a certain period.

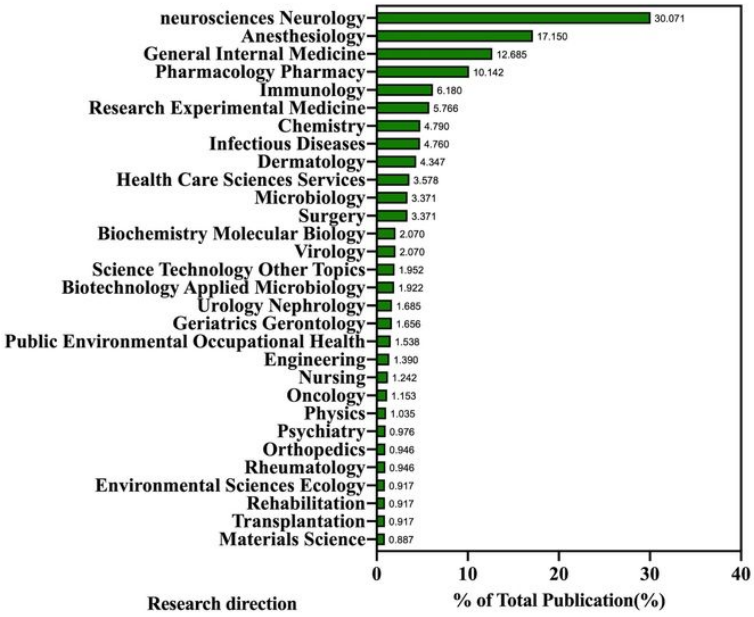

Figure 5

The top 30 category exploration map.

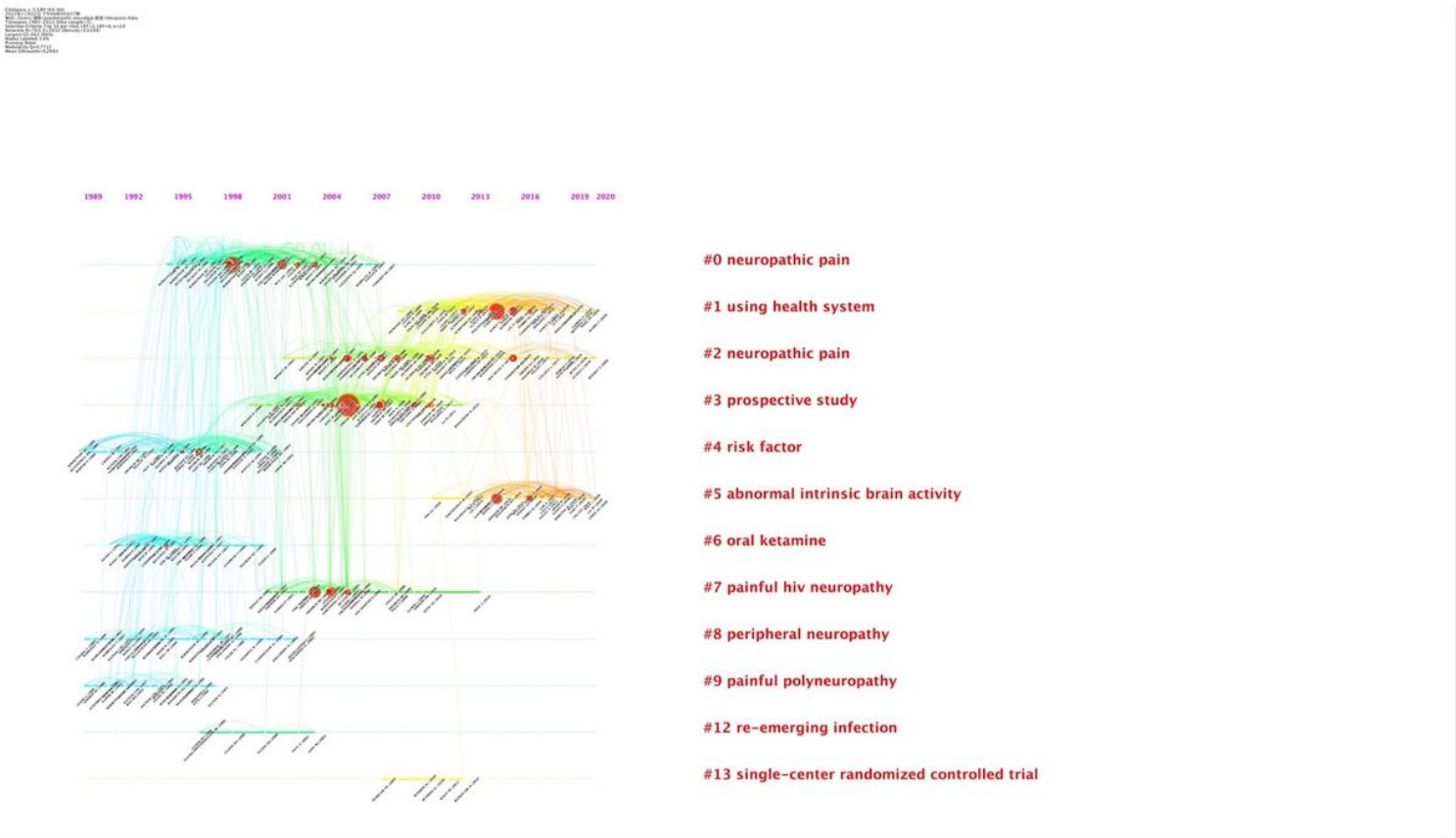

Figure 6

Reference timeline view. Node size and color represents total number of citations and a single time slice, respectively. Lines of different colors show that the two references were co-cited in an article.

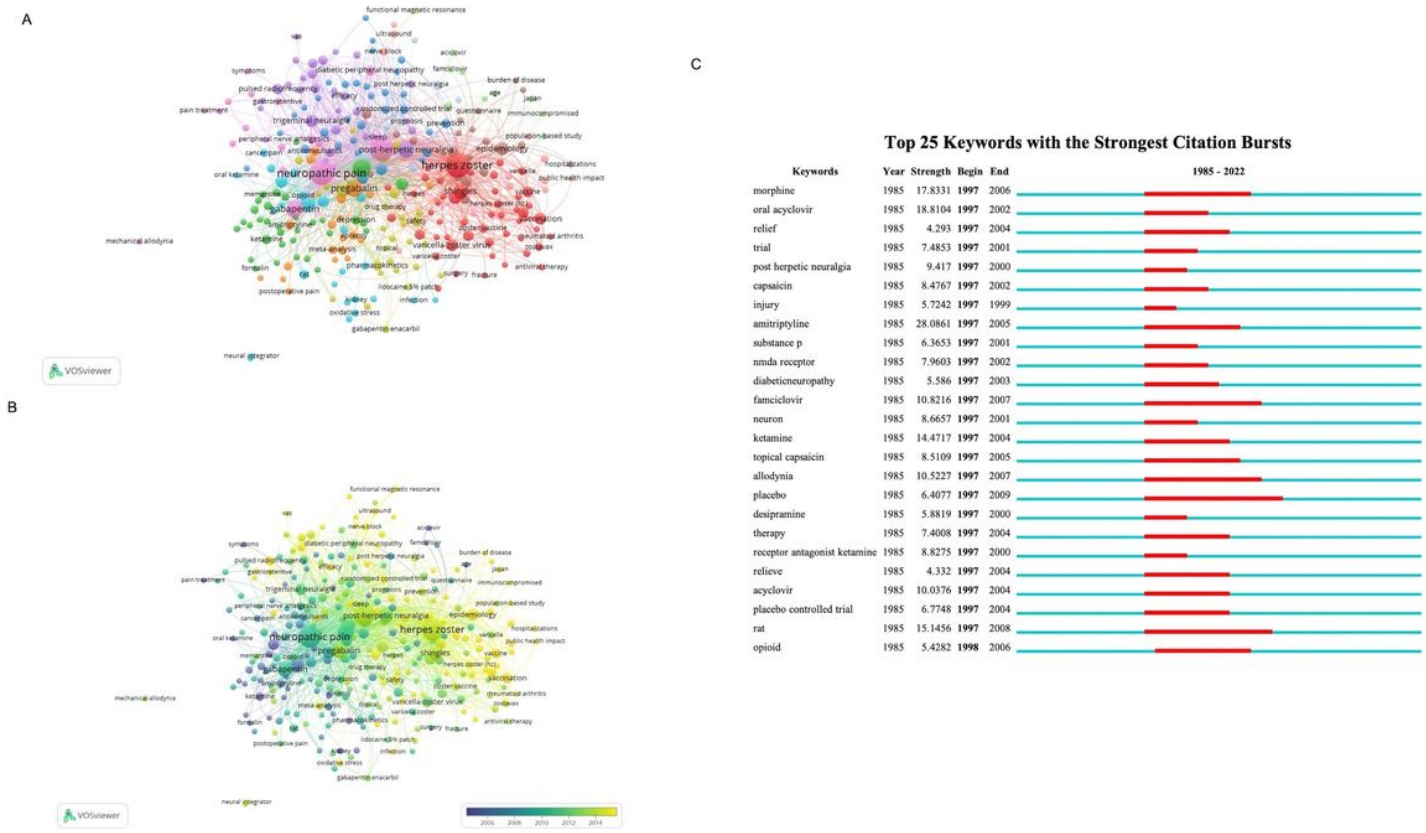

Figure 7

Keywords map. A) Keywords co-occurrence network. Node size and color represents the number of keywords and cluster. Lines of different colors show that the 2 keywords appear in an article. B) Keywords co-occurrence network of years. C) Top 25 keywords with the strongest citation bursts. Red bars mean that some keywords were cited frequently in a certain period.

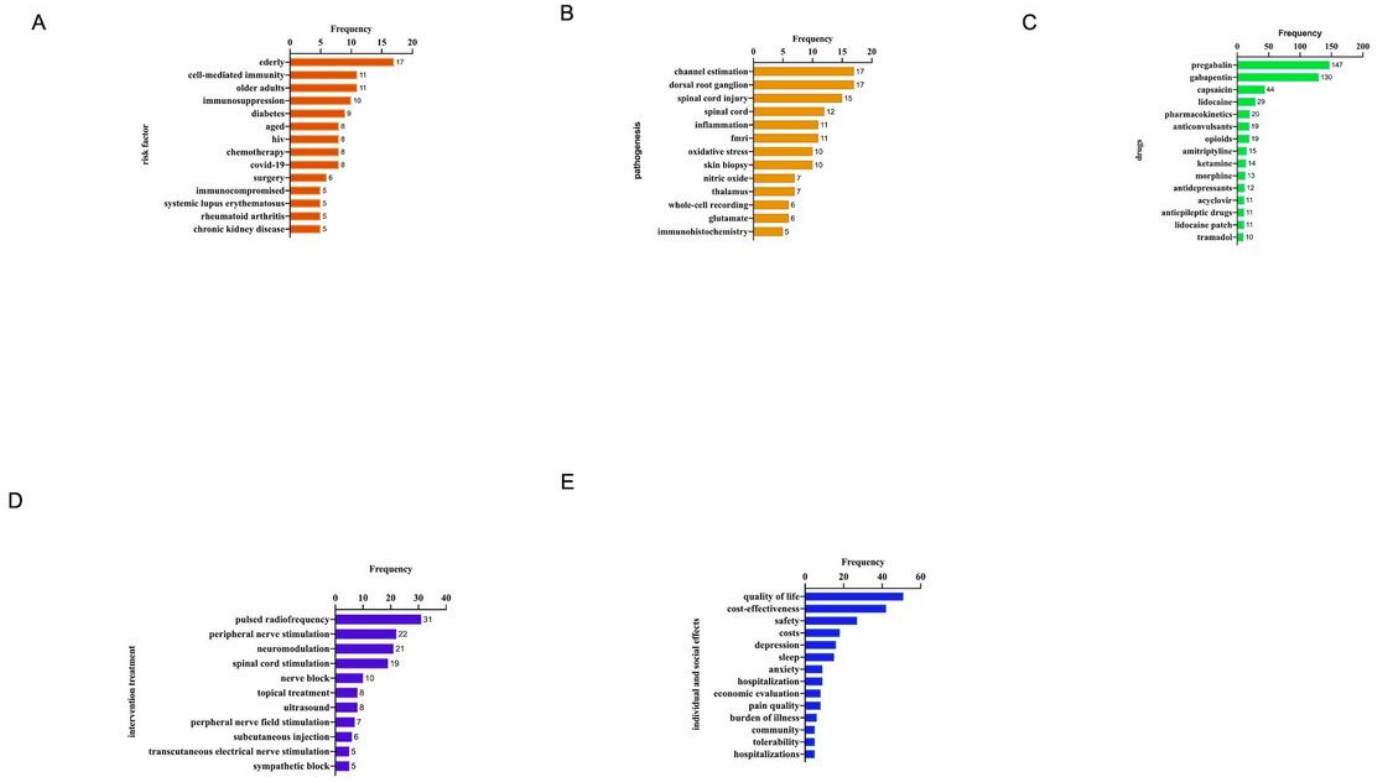

Figure 8

Artificial analysis of keywords. A) Risk factors. B) Pathogenesis. C) Drug treatment. D) Intervention treatment. E) Individual and social effects