

Knowledge Mapping and Research Hotspots of Generalized Pustular Psoriasis: A Bibliometric Analysis from 2003 to 2023

Lu Wei¹, Buxin Zhang², Li Wang², Juntao Xu², Aimin Liu^{1,2}

¹Department of Dermatology, Henan University of Chinese Medicine, Zhengzhou, Henan, People's Republic of China; ²Department of Dermatology, Henan Province Hospital of Traditional Chinese Medicine, The Second Affiliated Hospital of Henan University of Chinese Medicine, Zhengzhou, Henan, People's Republic of China

Correspondence: Aimin Liu, Department of Dermatology, Henan Province Hospital of Traditional Chinese Medicine, The Second Affiliated Hospital of Henan University of Chinese Medicine, No. 6, Dongfeng Road, Jinshui District, Zhengzhou city, Henan Province, 450053, People's Republic of China, Tel +86 13592603226, Fax +86-371-60973329, Email hnzylam@126.com

Background: Generalised pustular psoriasis (GPP) is a chronic inflammatory skin disease. We aimed to visualize the research hotspots and trends of GPP using bibliometric analysis to enhance our comprehension of the future advancements in both basic science and clinical research.

Methods: Relevant publications from July 2003 to July 2023 were obtained from the Web of Science Core Collection on July 12, 2023. The analysis of countries, institutions, authors, references, and keywords associated with this subject was conducted through the utilisation of CiteSpace 6.2.R4, VOSviewer 1.6.18, and Microsoft Excel 2019.

Results: A total of 578 papers were analyzed, authored by 2758 researchers from 191 countries/regions and 1868 institutions, published in 174 academic journals. There was an overall upward trajectory in the volume of annual publications, accompanied by a gradual intensification of research interest in GPP. The United States, UDICE-French Research Universities, and Akiyama M of Nagoya University were the most productive and influential country, institution, and author, respectively. The *Journal of Dermatology* ranked first with the highest publications, and the *Journal of the American Academy of Dermatology* received the most citations. High-frequency keywords included “generalized pustular psoriasis”, “psoriasis, interleukin-36”, “plaque psoriasis”, “skin-disease”, and “antagonist deficiency”. Recent research focuses have included “safety”, “secukinumab”, “spesolimab”, “ap1s3 mutations”, and “interleukin-36”. Burst detection analysis of keywords showed that “moderate”, “ixekizumab treatment”, “mutations”, “efficacy”, and “safety” are current research frontiers in this field.

Conclusion: This bibliometric analysis delineated the landmark publications in GPP that have defined current research hotspots and development trends, notably the applications, efficacy, and safety of biological agents. Future research endeavors are warranted to explore other biological therapeutic options for both acute GPP and the long-term management of chronic GPP.

Keywords: generalised pustular psoriasis, psoriasis, interleukin-36, developing trends, bibliometric analysis

Introduction

Psoriasis is a chronic-inflammatory cutaneous disease that exhibits diverse clinical manifestations. The most common form of psoriasis, known as plaque psoriasis, primarily arises from adaptive immune system abnormalities.¹ Generalized pustular psoriasis (GPP), a more severe and infrequent subtype of psoriasis that may be life-threatening, is associated with excessive activation of the innate immune system. GPP is characterized by widespread eruptions of sterile, macroscopic pustules that manifest with or without signs of systemic inflammation.^{2,3} The management of GPP poses significant challenges, mostly due to the difference in pathogenesis compared to plaque psoriasis.⁴ It is now understood that GPP has an indirect impact on the economy through exacerbation of work productivity impairment.⁵ However, a lack of global consensus on the clinical criteria for GPP diagnosis and treatment goal establishment persists. However, no consensus has been reached regarding the clinical criteria for diagnosing GPP and establishing treatment goals. Accordingly, a comprehensive exploration of GPP is crucial, as it will facilitate the development of novel concepts for clinical prevention and treatment approaches.

Bibliometric analysis is a prominent form of scholarly investigation that assesses intrinsic relationships and dissemination patterns within the study literature, aiming to identify the most popular subjects, hotspots, and rapidly growing subfields, facilitating knowledge sharing among experts.⁶

This study aims to provide physicians and researchers with a comprehensive historical analysis of GPP hotspots and scientific advancements over the previous twenty-year period, based on the findings derived from data analysis in the existing literature. The research findings will contribute to a deeper understanding of the subject, hence generating novel concepts for basic research, clinical prevention, and treatment strategies.

Methods

The Web of Science Core Collection (WoSCC) is a globally recognized and influential citation index database that covers a broad spectrum of research types and is commonly employed in bibliometric research.⁷ The search query was formulated as TS = (“generalized pustular psoriasis”), encompassing a time frame spanning from July 12, 2003, to July 12, 2023. The searches and data exports were performed on a certain date (July 12, 2023) due to the dynamic nature of metrics that continually fluctuate over time. The language utilized in the publications was English. The possible publication types were limited to “articles” and “reviews”. Two researchers conducted an independent secondary screening of the retrieved articles by assessing the titles and abstracts to ensure they were relevant to the research subject. A third researcher resolved discrepancies and uncertainties during the selection process. Details of the process of the literature inclusion and exclusion process are presented in Figure 1.

To facilitate visual analysis, all relevant data collected from WoSCC were exported to Microsoft Excel 2019, VOSviewer 1.6.19, and CiteSpace 6.2.R4.

Results

The Trend of Publication Outputs

Figure 2 illustrates the correlation between the quantity of articles published over specific time periods and the overall trajectory of research advancement within this discipline. Between 2003 and 2009, there was a notable dearth in publishing outputs, indicating that research during this period was in its nascent phase. From 2010 to 2021, despite

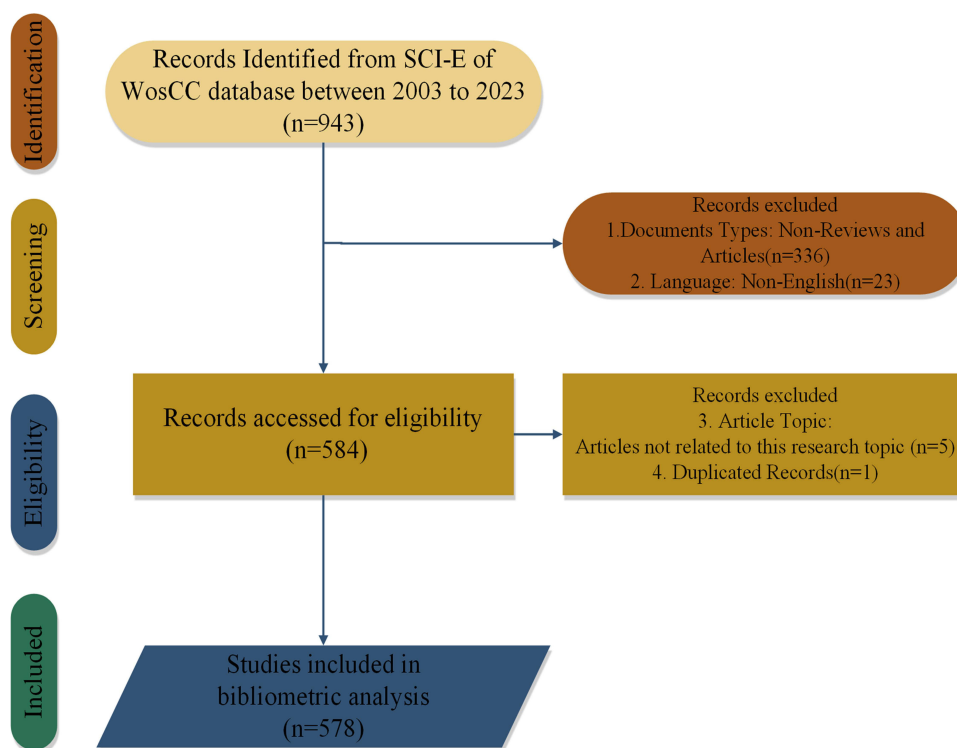


Figure 1 The flow diagram of literature enrollment and data screening.

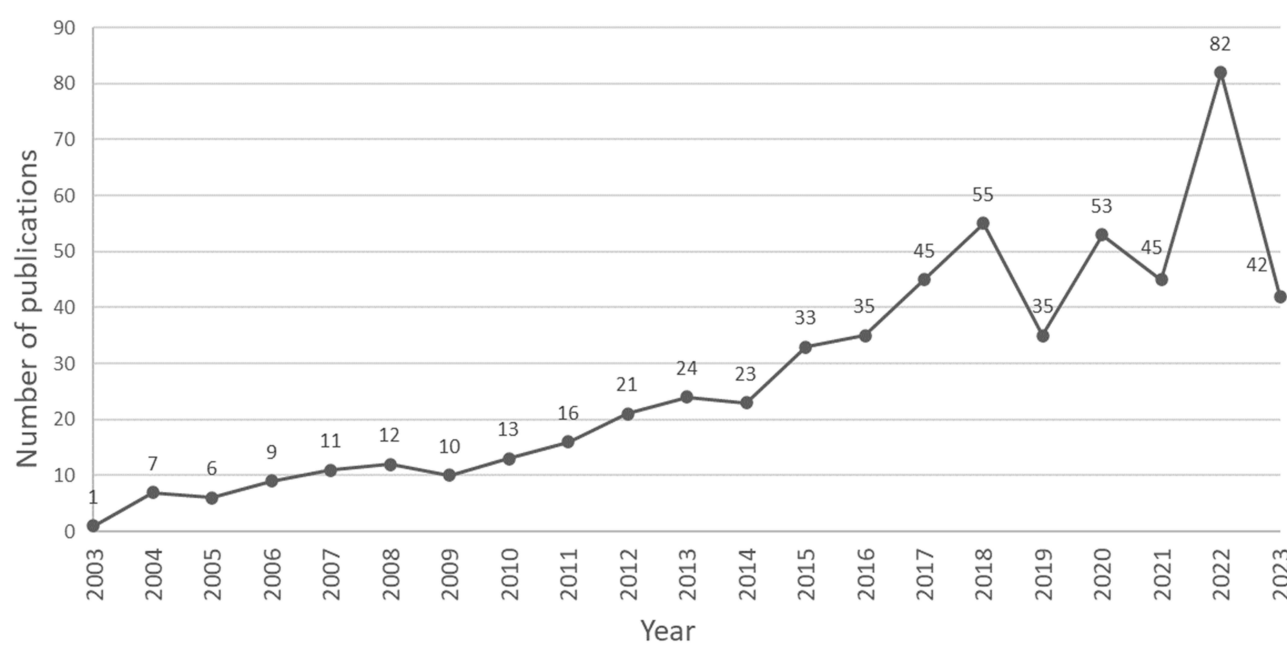


Figure 2 The annual number of publications related to GPP (2003–2023).

occasional fluctuations, the quantity of published papers displayed an overall increasing trend, signifying growing interest in GPP. Global interest peaked in 2022, with 82 publications. As of July 12, 2023, the total number of articles now stands at 42. However, it is anticipated that this figure will undergo further growth in the future.

Distribution of Countries and Institutions

A total of 578 scholarly publications originated from 191 nations and were affiliated with 1868 academic organizations. According to the data presented in [Table 1](#), the United States contributed the highest quantity of publications (161, 19.1%), followed by Japan (115, 13.7%), and China (93, 11.1%). International networks of cooperation are depicted in [Figure 3A](#). Germany (0.76), the United States (0.38), and Italy (0.29) had the highest centrality scores.

Table 1 Ranking of Top-10 Countries That Have Published the Most Article from 2003 to 2023

Rank	Articles Counts	Centrality Score	Country
1	161	0.38	USA
2	115	0.23	Japan
3	93	0.16	China
4	63	0.76	Germany
5	43	0.06	United Kingdom
6	42	0.29	Italy
7	41	0.26	France
8	33	0	Switzerland
9	21	0.29	Malaysia
10	18	0	Canada

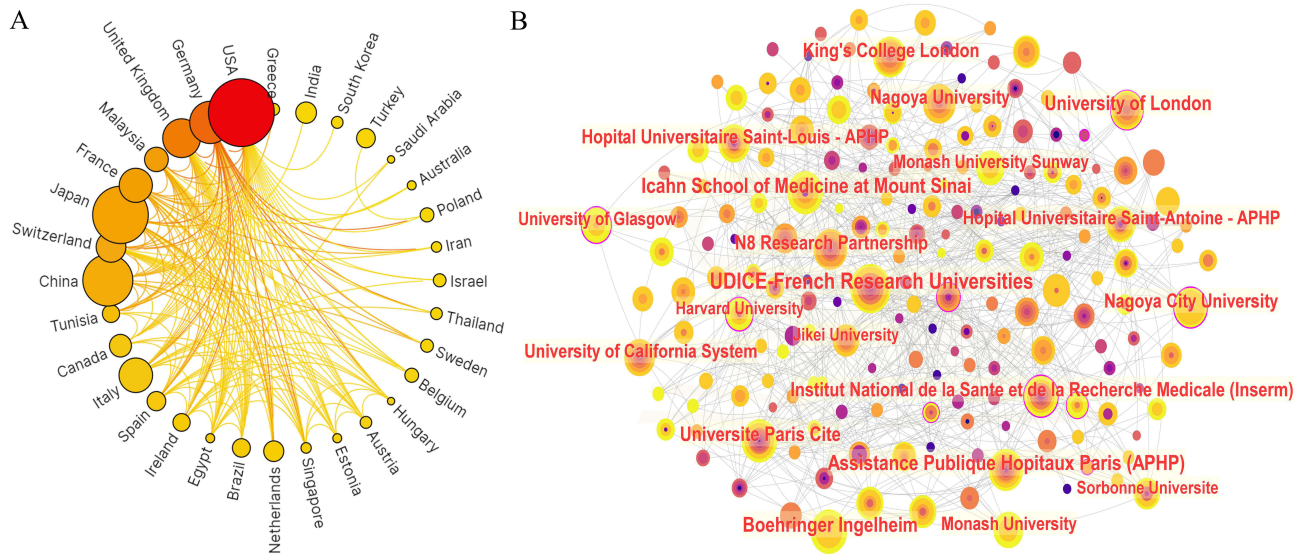


Figure 3 (A) Cooperation network of prolific countries/regions. (B) Visualization map of institutions' cooperative relations.

Table 2 illustrates the top ten most prolific organizations. UDICE-French Research Universities published 27 papers, making it the leading research institution in terms of contribution to this area. France is home to four of the top ten institutions. Figure 3B displays the institutionalized network map of collaboration. Only a handful of institutions demonstrated active cooperation, like UDICE-French Research Universities and Harvard University. However, numerous nations and research institutes were geographically dispersed and exhibited limited collaboration.

Authors and Co-Cited Authors

The literature on GPP included 2758 authors. For the cooperation network analysis, only authors with a frequency of at least four times were included, resulting in a subset of 94 authors (Figure 4). Table 3 lists the top ten most prolific scholars. Akiyama M demonstrated the highest level of scholarly productivity, having authored 15 articles. Bachelez H achieved the highest citation ranking (784 citations). Akiyama M, Burden AD, and Morita A had the highest H-index value. Despite not ranking first in terms of article publication, Morita A occupied a central position in the network, displaying strong collaborative ties with other research groups.

Table 2 Ranking of Top-10 Institutions from 2003 to 2023

Rank	AC	Institution	Country	CS
1	27	UDICE-French Research Universities	France	0.09
2	21	Assistance Publique Hopitaux Paris (APHP)	France	0.09
3	21	Icahn School of Medicine at Mount Sinai	USA	0.06
4	20	Boehringer Ingelheim	Germany	0.02
5	19	University of London	The United Kingdom	0.11
6	18	Universite Paris Cite	France	0.04
7	17	N8 Research Partnership	The United Kingdom	0.07
8	17	Institut National de la Sante et de la Recherche Medicale (Inserm)	France	0.38
9	17	King's College London	The United Kingdom	0.08
10	16	Nagoya City University	Japan	0.21

Abbreviations: AC, articles counts; CS, centrality score.

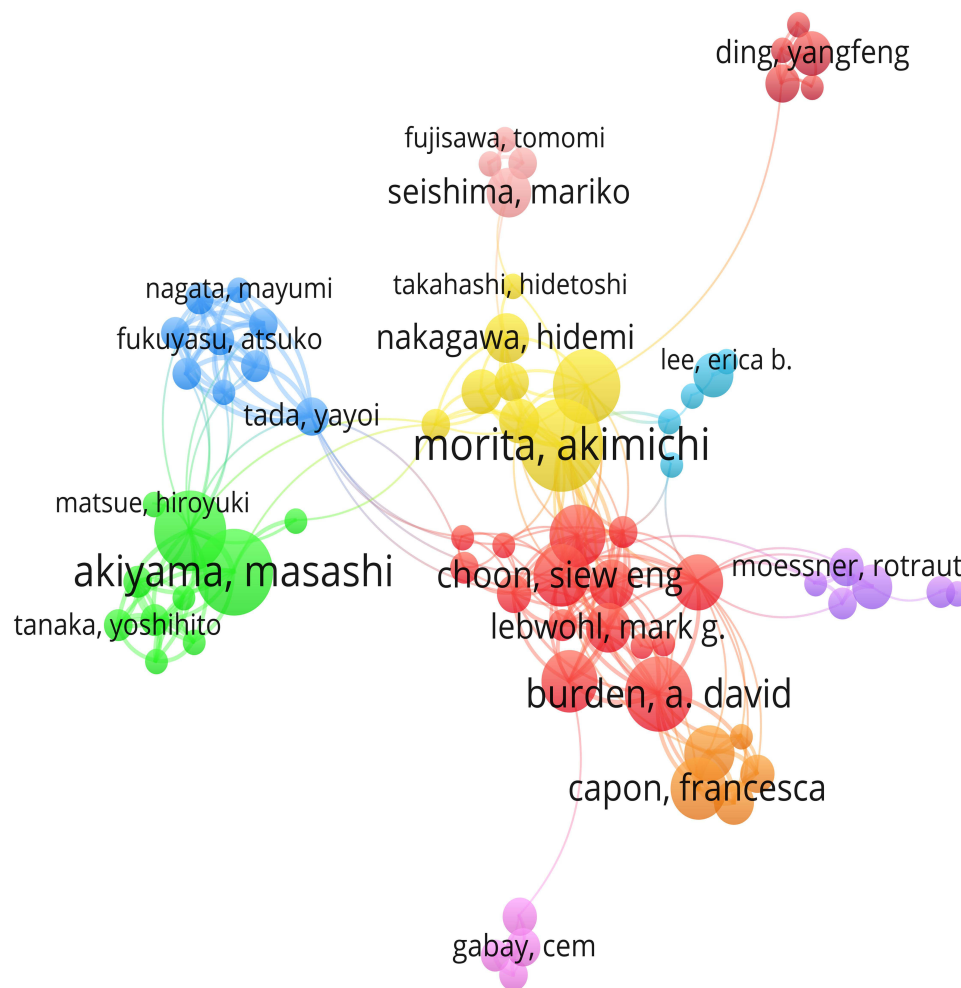


Figure 4 Collaborative network map among authors.

Analysis of Journals and Cited Journals

A total of 174 journals were considered relevant for this study. The top ten most prolific journals are detailed in Table 4, with a predominant focus on clinical dermatology. In this respect, the *Journal of Dermatology* led in publications, accounting for 11.28% of the total (65 publications).

Among the top ten journals, the *Journal of the American Academy of Dermatology* held the highest impact factor (IF) at 13.8, with six journals situated in the first quartile (Q1) and four journals having an IF of 5.0 or higher, indicating that articles related to GPP demonstrate high quality and substantial academic merit.

The application of a dual-map overlay technique facilitated the visualization of subject distribution and interconnections among various academic journals. Figure 5 illustrates five major citation relationships. For instance, the yellow route indicates that publications in journals focusing on molecular, biology and genetics tend to receive citations from journals in the fields of molecular biology and immunology ($z=4.341$, $f=29780$).

Analysis of Keyword Co-Occurrence and Bursts

The entries that were retrieved yielded a total of 1840 keywords. Figure 6A presents the keyword co-occurrence visualization map, with each node's size representing the frequency of occurrence. According to Table 5, the most frequently occurring keywords, excluding GPP ($n=385$), were psoriasis ($n=185$), interleukin (IL) -36 ($n=121$), plaque psoriasis ($n=80$), skin-disease ($n=78$), and antagonist deficiency ($n=70$), suggesting these areas were focal points in GPP studies.

Table 3 Ranking of Top-10 Most Productive Authors from 2003 to 2023

Rank	Author	AC (100%)	CS	TNC	ANC	H-Index
1	Akiyama, Masashi	15(2.6%)	0.09	477	31.80	52
2	Morita, Akimichi	13(2.2%)	0.18	410	31.54	40
3	Okubo, Yukari	11(1.9%)	0.04	194	17.64	19
4	Sugiura, Kazumitsu	11(1.9%)	0.05	512	46.55	29
5	Burden, A David	11(1.9%)	0.03	262	23.82	48
6	Bachelez, Herve	10(1.7%)	0.08	784	78.40	26
7	Choon, Siew Eng	9(1.6%)	0.07	77	8.55	24
8	Capon, Francesca	9(1.6%)	0	637	70.78	39
9	Thoma, Christian	8(1.4%)	0.01	61	7.63	22
10	Wu, Jashin J	8(1.4%)	0.04	520	65.00	39

Abbreviations: AC, articles count; CS, centrality score; TNC, total number of citations; ANC, average number of citations.

Table 4 Ranking of Top-10 Most Productive Journals from 2003 to 2023

Rank	Journal	AC	JCR	IF	TNC	MNC	H-Index
1	Journal of Dermatology	65	Q2	3.1	1437	22.11	20
2	Journal of the European Academy of Dermatology and Venereology	24	Q1	9.2	716	29.83	13
3	Journal of Dermatological Treatment	18	Q2	2.9	275	15.28	11
4	American Journal of Clinical Dermatology	17	Q1	7.3	432	25.42	12
5	British Journal of Dermatology	16	Q1	10.3	942	58.88	13
6	Dermatology	16	Q2	3.4	296	18.50	10
7	Journal of the American Academy of Dermatology	16	Q1	13.8	1485	92.81	15
8	Dermatologic Therapy	15	Q1	3.6	171	11.40	8
9	Dermatology and Therapy	13	Q2	3.4	126	9.69	5
10	Experimental Dermatology	13	Q1	3.6	70	5.38	3

Abbreviations: AC, article count; JCR, journal citation reports; IF, impact factor; TNC, total number of citations; MNC, mean number of citations.

The keywords were classified into four categories represented by differently colored circles based on the strength of connections between keywords (Figure 6A). The red cluster primarily represents GPP, encompassing terms like skin-disease, IL-1, nuclear transcription factor-kappa B (NF-κB), and inflammation. The yellow cluster is related to psoriasis (including cyclosporine, acitretin, and biologic agents). The blue clusters focus on plaque psoriasis (including secukinumab, ustekinumab, and IL-17). The main keywords in the green cluster are IL-36 (including antagonist deficiency, psoriasis vulgaris, and ap1s3 mutations). The color intensity within the region suggested that the distribution of keywords follows a chronological order (Figure 6B). As shown in Figure 6B, the prominent areas of research in GPP over the past five years included safety, secukinumab, spesolimab, ap1s3 mutations, and IL-36. Furthermore, a visual representation of keyword co-occurrence based on time zones was generated (Figure 6C), aiding in observing the sequential emergence of research trends and the evolving directions of GPP research over time.

Figure 7 highlights the 20 most prominent keywords exhibiting significant citation bursts. Between 2003 and 2023, “efficacy” showed the greatest burst strength (9.5), followed by “safety” (9.2) and “childhood psoriasis” (7.02).

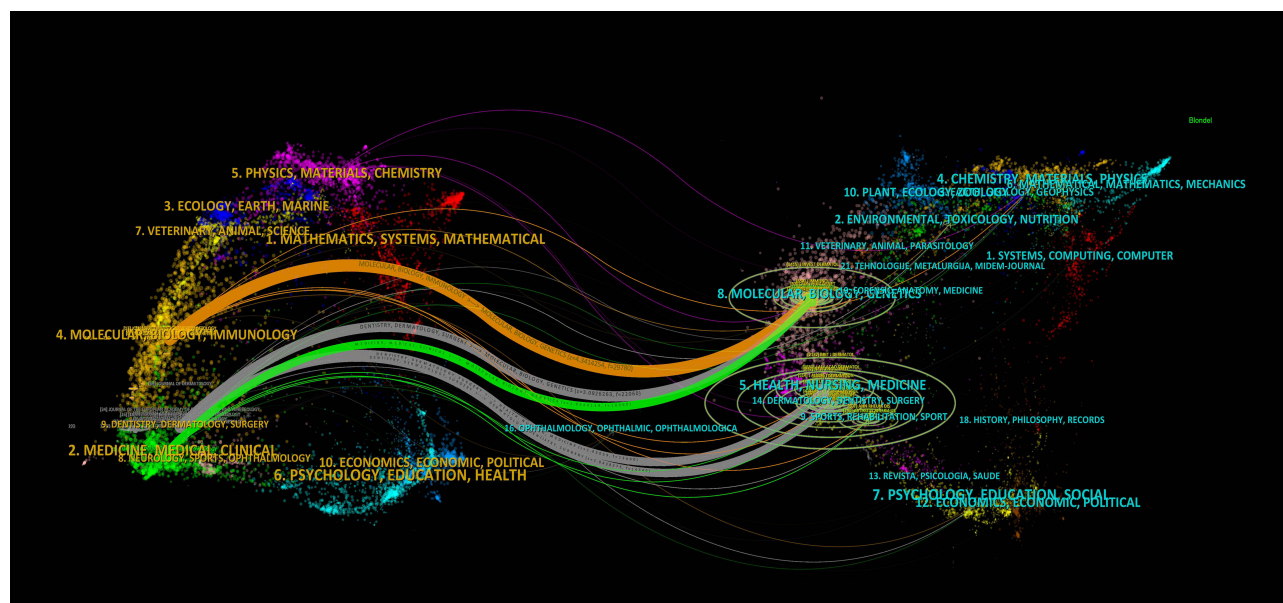


Figure 5 The dual-map overlay of journals on GPP.

Additionally, “moderate”, “ixelizumab treatment”, “mutations”, “efficacy”, and “safety” sustained prominence until 2023, indicating their relevance in current research trends.

Analysis of Co-Cited References and Reference Bursts

Table 6 lists the 10 most cited references. The paper published by Marrakchi et al⁸ in the *New England Journal of Medicine* (70) was the most referenced, indicating its significance as a foundational work in this particular field. Figure 8 displays the ten references with the most pronounced citation bursts, with the initial burst of co-cited references starting in 2011. The article with the strongest burst (33.72) was published by Marrakchi et al⁸ in 2011. Additionally, the paper titled “An update on generalized pustular psoriasis⁹” experienced a significant burst lasting until 2023.

The co-citation associations among references were visualized in a network with 280 nodes (references) and 324 linkages (Figure 9A). Figure 9B illustrates the 16 most prominent clusters in the reference co-citation network, mapping to the field's primary study subjects. The five most prominent clusters include "cathepsin g", "childhood psoriasis", "pustular psoriasis", "IL-36rn mutation", and "disease management". Figure 9C depicts the development of the sixteen largest clusters through time, shedding light on the changing scientific significance of co-cited references. The most recent clusters are "cathepsin g" (#0), "pustular psoriasis" (#2), "disease management" (#4), "new era" (#6), and "erythrodermic psoriasis" (#11).

Discussion

Researchers can gain a deeper understanding of the current state of research on a specific topic and anticipate future trends with the help of bibliometrics. This study is the first attempt to investigate GPP through the utilization of bibliometric analysis and visualization techniques.

General Information

A total of 578 papers were published in 174 journals between 2003 and 2023. These papers were authored by 2758 individuals affiliated with 273 institutions spanning 57 countries. The data presented in [Figure 2](#) illustrates a general upward trend in the overall quantity of publications over the previous twenty years. GPP research has notably emerged as a prominent area of study in recent years, showcasing an excellent development trend. An examination of contributions by country highlights the United States as the leader, constituting 19.1% of overall publications. Germany, with the utmost centrality of 0.53, serves as a bridge in global collaboration.

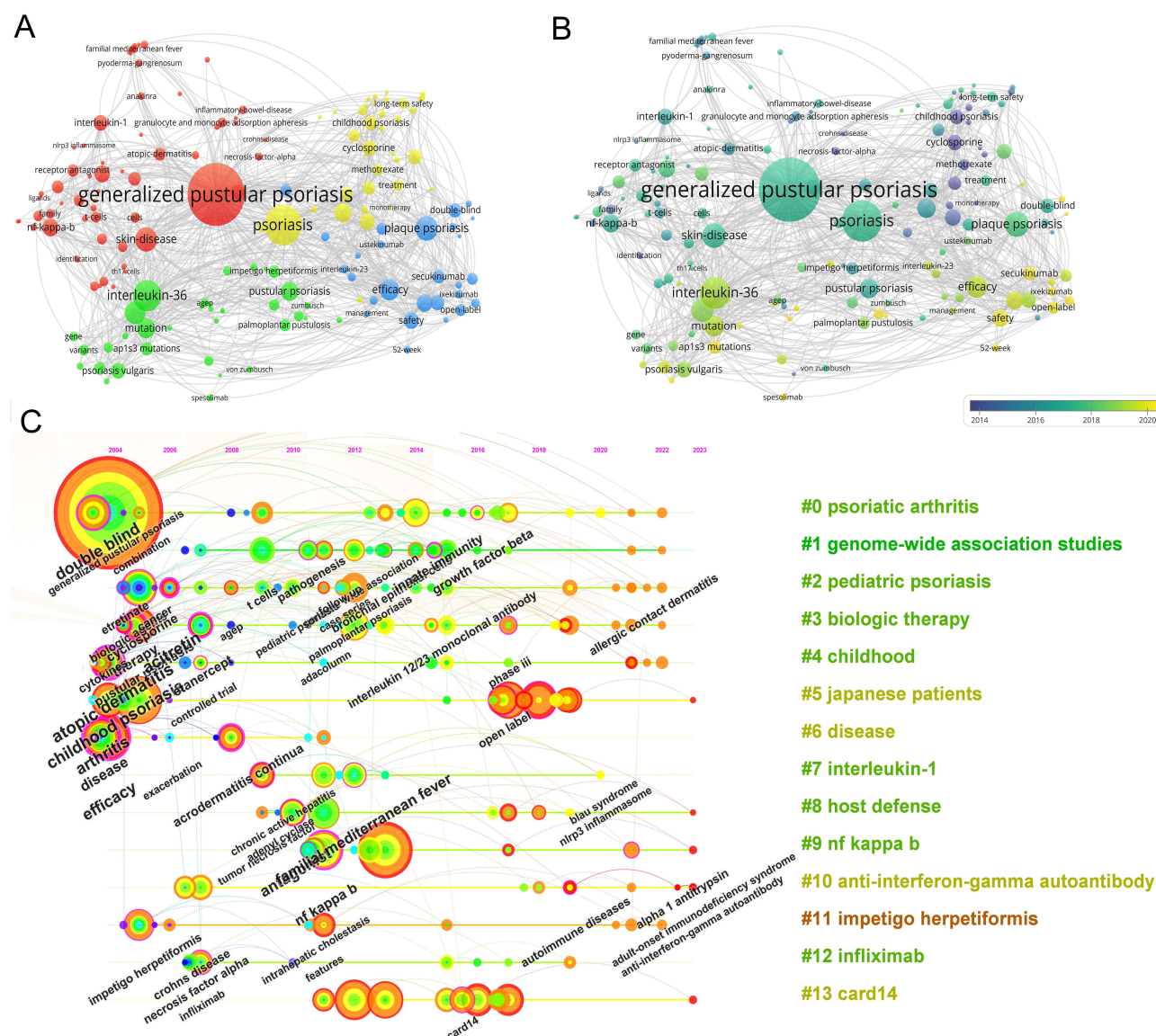


Figure 6 Keywords analysis for research of GPP (2003–2023). **(A)** Clustering co-occurrence map of keywords. **(B)** Distribution of keywords based on the average time of appearance. **(C)** Time-zone view of keyword co-occurrence.

Approximately 2000 institutions globally contributed to GPP research, with UDICE-French Research Universities demonstrating the highest productivity. Among the top ten research institutes, four were from France, with the Institut National de la Sante et de la Recherche Medicale having the highest impact. As depicted in Figure 3B, inter-institutional collaboration primarily occurs within national boundaries, lacking international interactions. This limitation has the potential to impede the progress and advancement of the discipline. Therefore, it is strongly recommended to coordinate research resources across relevant national departments to promote cooperation among research institutions.

Akiyama M was identified as the most prolific author in terms of published articles and possesses the highest H-index in this field. His research focuses on rare intractable hereditary skin diseases and inflammatory skin diseases.^{11–13} Interestingly, Bachelez H, despite a modest publication record of only 10 articles, was associated with the highest number of citations. The author cooperation network revealed the formation of many academic teams and robust collaboration among diverse research groups. Of the top 10 journals, six were situated within the first quartile of the Journal Citation Reports, with two possessing an IF exceeding 10, indicating a high standard of articles within this discipline.

An in-depth analysis of co-citation frequency indicates that Marrakchi S, Fujita H, and other representatives have a higher frequency of citation overall. The article authored by Marrakchi et al⁸ emerged as the most commonly co-

Table 5 Top 10 Keywords Related to GPP

Rank	Keyword	Cluster	TLS	Frequency
1	Generalized pustular psoriasis	Red	2109	385
2	Psoriasis	Yellow	1127	185
3	Interleukin-36	Blue	793	121
4	Plaque psoriasis	Green	634	80
5	Skin-disease	Red	475	78
6	Antagonist deficiency	Blue	468	70
7	Efficacy	Green	496	63
8	Mutation	Blue	331	56
9	Pustular psoriasis	Green	307	52
10	Therapy	Yellow	364	52

Abbreviation: TLS, total link strength.

cited publication. He found that an abnormality in the structure and function of IL-36Ra causes the unregulated release of inflammatory cytokines in GPP. The second most co-cited paper was a guideline for Japanese patients with GPP published by Fujita et al.¹⁰

Top 20 Keywords with the Strongest Citation Bursts

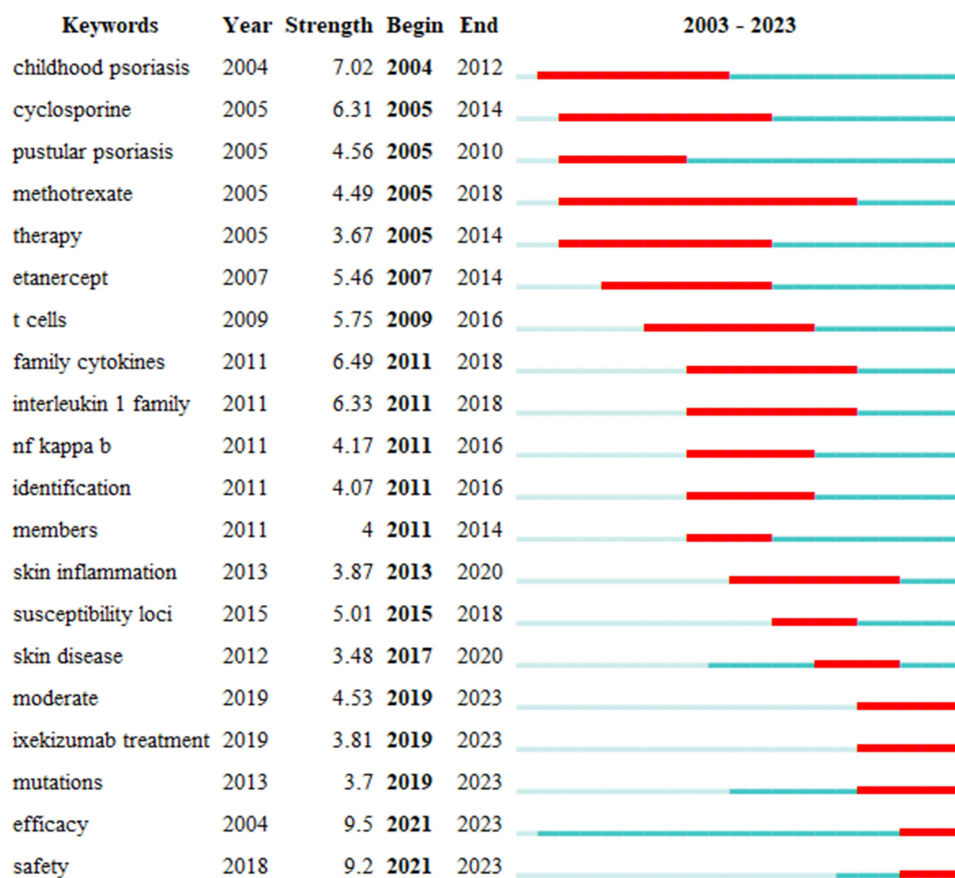
**Figure 7** Top 20 keywords with the strongest citation bursts related to GPP (2003–2023).

Table 6 Top-10 Most Co-Cited References from 2003 to 2023

Rank	Title	Author	Year	Journal	CF
1	Interleukin-36-receptor antagonist deficiency and generalized pustular psoriasis ⁸	Marrakchi S	2011	New England Journal of Medicine	70
2	Japanese guidelines for the management and treatment of generalized pustular psoriasis: The new pathogenesis and treatment of GPP ¹⁰	Fujita H	2018	The Journal of Dermatology	68
3	IL-1 and IL-36 are dominant cytokines in generalized pustular psoriasis ²¹	Johnston A	2017	The Journal of Allergy and Clinical Immunology	66
4	Clinical and genetic differences between pustular psoriasis subtypes ³²	Twelves S	2019	The Journal of Allergy and Clinical Immunology	62
5	European consensus statement on phenotypes of pustular psoriasis ³	Navarini AA	2017	Journal of the European Academy of Dermatology and Venereology	62
6	Inhibition of the Interleukin-36 Pathway for the Treatment of Generalized Pustular Psoriasis ⁵⁰	Bachelez H	2019	New England Journal of Medicine	57
7	Mutations in IL36RN/IL1F5 are associated with the severe episodic inflammatory skin disease known as generalized pustular psoriasis ⁵¹	Onoufriadis A	2011	American Journal of Human Genetics	56
8	Efficacy and safety of brodalumab in patients with generalized pustular psoriasis and psoriatic erythroderma: results from a 52-week, open-label study ⁴¹	Yamasaki K	2017	The British journal of dermatology	53
9	Efficacy and safety of ixekizumab treatment for Japanese patients with moderate to severe plaque psoriasis, erythrodermic psoriasis and generalized pustular psoriasis: Results from a 52-week, open-label, phase 3 study (UNCOVER-J) ⁴⁰	Saeki H	2017	The Journal of Dermatology	48
10	Guselkumab, a human interleukin-23 monoclonal antibody in Japanese patients with generalized pustular psoriasis and erythrodermic psoriasis: Efficacy and safety analyses of a 52-week, phase 3, multicenter, open-label study ⁴⁴	Sano S	2018	The Journal of Dermatology	44

Abbreviation: CF, citation frequency.

Emerging Topics

Pathogenesis

Fifty percent of patients with GPP also have concomitant psoriasis vulgaris (also known as plaque psoriasis).^{14,15} GPP has traditionally been viewed as a subset of psoriasis vulgaris, but more recent literature recognizes GPP as having

Top 10 References with the Strongest Citation Bursts

References	Year	Strength	Begin	End	2003 - 2023
Marrakchi S, 2011, NEW ENGL J MED, V365, P620, DOI 10.1056/NEJMoa1013068, DOI	2011	33.72	2011	2016	
Onoufriadis A, 2011, AM J HUM GENET, V89, P432, DOI 10.1016/j.ajhg.2011.07.022, DOI	2011	26.69	2011	2016	
Carrier Y, 2011, J INVEST DERMATOL, V131, P2428, DOI 10.1038/jid.2011.234, DOI	2011	11.07	2011	2016	
Towne JE, 2011, J BIOL CHEM, V286, P42594, DOI 10.1074/jbc.M111.267922, DOI	2011	10.58	2011	2016	
Sugiura K, 2013, J INVEST DERMATOL, V133, P2514, DOI 10.1038/jid.2013.230, DOI	2013	17.63	2015	2018	
Imafuku S, 2016, J DERMATOL, V43, P1011, DOI 10.1111/1346-8138.13306, DOI	2016	13.16	2017	2022	
Fujita H, 2018, J DERMATOL, V45, P1235, DOI 10.1111/1346-8138.14523, DOI	2018	11.54	2019	2023	
Navarini AA, 2017, J EUR ACAD DERMATOL, V31, P1792, DOI 10.1111/jdv.14386, DOI	2017	11.06	2019	2023	
Twelves S, 2019, J ALLERGY CLIN IMMUN, V143, P1021, DOI 10.1016/j.jaci.2018.06.038, DOI	2019	11.02	2019	2023	
Gooderham MJ, 2019, EXPERT REV CLIN IMMUN, V15, P907, DOI 10.1080/1744666X.2019.1648209, DOI	2019	11.3	2021	2023	

Figure 8 Top 15 references with the strongest citation bursts related to field of GPP (2003–2023).

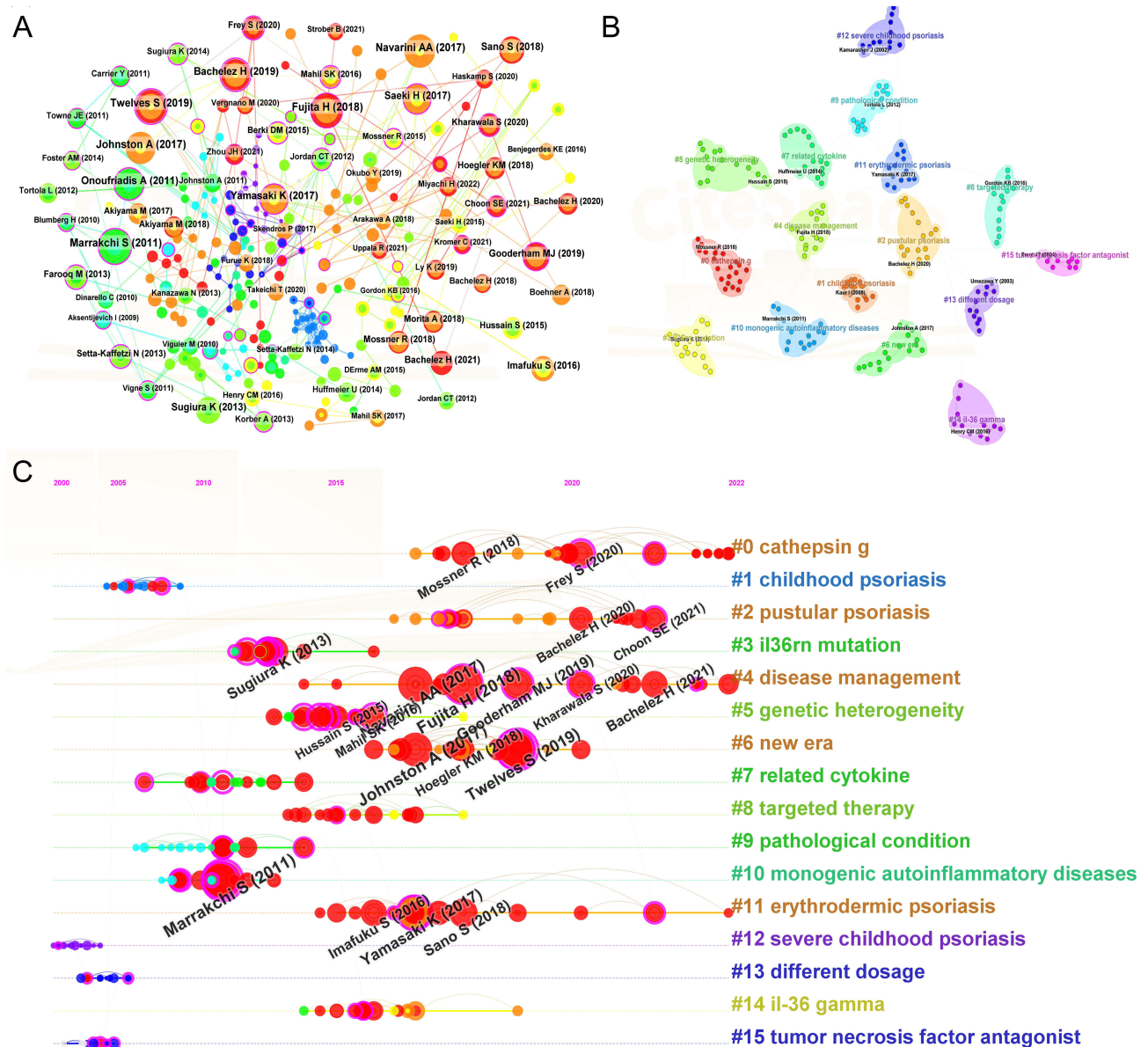


Figure 9 Analysis of co-cited references in the field of GPP (2003–2023). **(A)** The network of co-cited references. **(B)** Clustering visualization map of the co-cited references. **(C)** Timeline visualization map of the co-cited references.

a unique etiology, phenotypically, and pathophysiology.^{16,17} Mechanisms linked to dysregulation of the innate immune system in GPP include the disruption of the IL-36 inflammatory pathway, the stimulation of inflammatory keratinocyte responses, and the recruitment of neutrophils.¹⁸ The pathogenesis of psoriasis vulgaris is mostly influenced by the adaptive immune system, wherein the cytokine IL-17 plays a substantial role.^{19,20} In contrast to plaque psoriasis lesions, GPP lesions show elevated levels of neutrophilic chemokines and neutrophil and monocyte transcripts.²¹ In Japan, 82% of solely diagnosed GPP patients exhibit IL-36 receptor antagonist (IL36RN) mutations. In contrast, a considerably lower percentage (10%) of Japanese patients diagnosed with both GPP and psoriasis vulgaris presented with the same mutation.²² Genetic testing, particularly for IL36RN mutations is recommended for GPP diagnosis.

The relevance of genetic predisposition in the etiology of GPP has been demonstrated in several familial case studies. Defects in genes such as IL36RN,²³ caspase recruitment domain family member 14 protein (CARD14),²⁴ adaptor related protein complex 1 subunit sigma 3 (AP1S3),²⁵ myeloperoxidase (MPO),²⁶ and serpin peptidase inhibitor clade A member 3 (SERPINA3)²⁷ —have been identified in a subset of GPP patients.

The first pathogenic variant associated with GPP was the homozygous IL36RN mutation.²⁸ This mutation has been reported to inhibit the function of IL-36Ra, leading to increased activation of signal pathways linked with IL-36 and exacerbating GPP inflammations.⁸ Mutations in the CARD14 gene have also been linked to GPP development.¹⁸ CARD14 stimulates NF- κ B signaling, upregulating chemokine ligand 20 (CCL20) and IL-8 gene expression in keratinocytes, triggering the recruitment of inflammatory cells and causing epidermal inflammation.²⁹ AP1S3 mutations have been associated with GPP, leading to the destabilization of the adaptor protein complex 1²⁵. Keratinocytes with AP1S3 mutations exhibit reduced autophagosome production, resulting in p62 accumulation.³⁰ Elevated p62 levels heighten NF- κ B signalling, leading to the upregulation of IL-36 α and overstimulation of the IL-36 pathway.³¹ In addition, it is worth noting that AP1S3 mutations in the context of GPP, palmoplantar pustulosis, and acetylcholine may exhibit varying penetrance influenced by sex-specific variables. This is supported by the observation that nearly all individuals carrying AP1S3 disease alleles were female, though statistical significance was not achieved ($p = 0.06$).³² It has been established that the gene SERPINA3 is responsible for encoding alpha-1 anti-chymotrypsin, which is an inhibitor of cathepsin G. Cathepsin G is a protease released by neutrophils and plays a role in the activation of IL-36 precursors.²⁷

Treatment

A globally recognized therapeutic guidance for GPP is still lacking, and treatment approaches often reflects the recommendations for plaque psoriasis.³³ Current GPP treatment alternatives can be divided into two main groups: biological and non-biological systemic agents. Immunosuppressive medications, such as corticosteroids, acitretin, cyclosporine, and methotrexate, are commonly used as first-line therapies to suppress acute inflammation GPP.³⁴ However, there is limited, weak evidence for their clinical efficacy in GPP patients.

Biological agents have received approval for the treatment of GPP, and several clinical research studies have substantiated the efficacy and safety of biologics in treating GPP. At present, only one GPP-specific treatment. Spesolimab, a monoclonal antibody targeting the human IL-36 receptor, has recently been approved for GPP disease.³⁵ Spesolimab is not only the only on-label biologic for GPP management but is also the first biologic medicine licensed for this usage.³⁶ Research by Potestio et al³⁷ indicated the effectiveness and generally positive safety profile of spesolimab in patients with a GPP flare. Further research is warranted for a comprehensive understanding of spesolimab's effectiveness, safety, and long-term results in GPP patients.

Antagonistic antibodies targeting the IL-36 receptor have the potential to impede the signaling system responsible for triggering active GPP flares. Anakinra, a recombinant IL-1 receptor antagonist, has shown efficacy in GPP treatment in case reports.³⁸ Secukinumab, ixekizumab, and brodalumab, all three of these biological drugs are inhibitors of IL-17A and IL-17RA, have been approved for use in patients with GPP in Japan.^{39–41} Bimekizumab, a monoclonal antibody that specifically binds to and inhibits the activity of IL-17 A and F, has been demonstrated efficacy and safety in plaque psoriasis management.⁴² Hagino et al⁴³ documented the effective resolution of two GPP cases following bimekizumab treatment. The synthesis of IL-17 is reportedly regulated by IL-23, which subsequently induces the production of IL-36R agonists, leading to excessive activation of the IL-36 pathway.¹⁷ Guselkumab, a monoclonal antibody targeting human IL-23, was demonstrated to be effective and safe in patients with GPP and erythrodermic psoriasis.⁴⁴ Risankizumab, a new IL-23p19 inhibitor, has shown promise in the treatment of GPP.^{45,46} Ustekinumab, a monoclonal antibody inhibiting IL-12 and IL-23, has demonstrated efficacy in a patient diagnosed with GPP.⁴⁷ Tumor necrosis factor inhibitors, including adalimumab,⁴⁸ infliximab,⁴⁹ and certolizumab pegol, were primarily authorized for GPP management in Japan based on empirical evidence from individual case reports.

Limitations

This study exhibits inherent deficiencies and constraints typical in bibliometrics. Initially, this investigation exclusively accessed the widely utilized WOSCC database, which may have led to the inclusion of incomplete and biased research. Indeed, our findings could vary if alternative databases were employed. Additionally, our study exclusively focused on articles and reviews published in English language, potentially limiting the comprehensiveness of our findings. Addressing these restrictions is imperative in future endeavors.

Conclusion

The quantity of scholarly articles in this particular discipline has exhibited a general upward trend over the years, indicating a noteworthy emphasis by researchers on the subject of GPP. Globally, the United States holds a prominent position as the leading country in GPP research. UDICE-French Research Universities stands out as the research institution exerting the most influence on academic accomplishments. Akiyama M has made significant contributions to the field of GPP. The *Journal of Dermatology* is widely recognized as the most influential journal in this domain. Despite the widespread engagement among institutes and authors globally in this area, there remains a necessity to enhance academic interchange and cooperation. Recent research focuses have explored topics such as “safety”, “secukinumab”, “spesolimab”, “ap1s3 mutations”, and “IL-36”. These research areas hold significant importance and serve as a foundational knowledge base for further investigations. The forefront of research in this field includes “moderate”, “ixekizumab treatment”, “mutations”, “efficacy”, and “safety”. As our understanding of the underlying mechanisms and genetic factors contributing to GPP has improved, the opportunity for specific biological therapy to enhance patient outcomes has increased. In conclusion, our study provides an objective and comprehensive analysis of research on GPP, offering significant insights for future investigations in related areas.

Abbreviations

GPP, Generalised pustular psoriasis; WoSCC, Web of Science Core Collection; CARD14, caspase recruitment domain family member 14 protein; AP1S3, adaptor related protein complex 1 subunit sigma 3; MPO, myeloperoxidase; SERPINA3, serpin peptidase inhibitor clade A member 3; CCL20, chemokine ligand 20; NF- κ B, nuclear transcription factor-kappa B.

Data Sharing Statement

Further information and requests for data may be directed to and will be fulfilled by the Lead Contact: Prof. Aimin Liu (hnzyliam@126.com).

Consent for Publication

The details of the manuscript can be published and all the authors providing consent have been shown the article contents to be published.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

All authors report no competing interests in this work.

References

1. Hu P, Wang M, Gao H, et al. The role of helper T cells in psoriasis. *Front Immunol*. 2021;12:788940. doi:10.3389/fimmu.2021.788940
2. Bachelez H. Pustular psoriasis: the dawn of a New Era. *Acta Derm Venereol*. 2020;100(3):87–93. doi:10.2340/00015555-3388
3. Navarini AA, Burden AD, Capon F, et al. European consensus statement on phenotypes of pustular psoriasis. *J Eur Acad Dermatol Venereol*. 2017;31(11):1792–1799. doi:10.1111/jdv.14386

4. Megna M, Camela E, Ruggiero A, et al. Use of biological therapies for the management of pustular psoriasis: a New Era? *Clin Cosmet Invest Dermatol*. 2023;16:1677–1690. doi:10.2147/ccid.S407812
5. Zimmermann TM, Hofmann P, Chiu GR. A narrative review of the socioeconomic burden associated with generalised pustular psoriasis. *Exper Dermatol*. 2023;32(8):1219–1226. doi:10.1111/exd.14841
6. Ellegaard O, Wallin JA. The bibliometric analysis of scholarly production: how great is the impact? *Scientometrics*. 2015;105(3):1809–1831. doi:10.1007/s11192-015-1645-z
7. Zhang J, Song L, Jia J, et al. Knowledge mapping of necroptosis from 2012 to 2021: a bibliometric analysis. *Front Immunol*. 2022;13:917155. doi:10.3389/fimmu.2022.917155
8. Marrakchi S, Guigue P, Renshaw BR, et al. Interleukin-36-receptor antagonist deficiency and generalized pustular psoriasis. *N Engl J Med*. 2011;365(7):620–628. doi:10.1056/NEJMoa1013068
9. Gooderham MJ, Van Voorhees AS, Lebwohl MG. An update on generalized pustular psoriasis. *Expert Rev Clin Immunol*. 2019;15(9):907–919. doi:10.1080/1744666x.2019.1648209
10. Fujita H, Terui T, Hayama K, et al. Japanese guidelines for the management and treatment of generalized pustular psoriasis: the new pathogenesis and treatment of GPP. *J Dermatol*. 2018;45(11):1235–1270. doi:10.1111/1346-8138.14523
11. Akiyama M. Pustular psoriasis as an autoinflammatory keratinization disease (AiKD): genetic predisposing factors and promising therapeutic targets. *J Dermatological Sci*. 2022;105(1):11–17. doi:10.1016/j.jdermsci.2021.11.009
12. Akiyama M, Takeichi T, Ikeda S, et al. Recent advances in clinical research on rare intractable hereditary skin diseases in Japan. *Keio J Med*. 2023. doi:10.2302/kjm.2023-0008-IR
13. Fukaura R, Akiyama M. Targeting IL-36 in inflammatory skin diseases. *BioDrugs*. 2023;37(3):279–293. doi:10.1007/s40259-023-00587-5
14. Prinz JC, Choon SE, Griffiths CEM, et al. Prevalence, comorbidities and mortality of generalized pustular psoriasis: a literature review. *J Eur Acad Dermatol Venereol*. 2023;37(2):256–273. doi:10.1111/jdv.18720
15. Löfvendahl S, Norlin JM, Schmitt-Egenolf M. Comorbidities in patients with generalized pustular psoriasis: a nationwide population-based register study. *J Am Acad Dermatol*. 2023;88(3):736–738. doi:10.1016/j.jaad.2022.09.049
16. Zheng M, Jullien D, Eyerich K. The prevalence and disease characteristics of generalized pustular psoriasis. *Am J Clin Dermatol*. 2022;23(Suppl 1):5–12. doi:10.1007/s40257-021-00664-x
17. Zhou J, Luo Q, Cheng Y, Wen X, Liu J. An update on genetic basis of generalized pustular psoriasis (Review). *Int J Mol Med*. 2021;47(6). doi:10.3892/ijmm.2021.4951
18. Sugiura K. The genetic background of generalized pustular psoriasis: IL36RN mutations and CARD14 gain-of-function variants. *J Dermatol Sci*. 2014;74(3):187–192. doi:10.1016/j.jdermsci.2014.02.006
19. Hawkes JE, Yan BY, Chan TC, Krueger JG. Discovery of the IL-23/IL-17 Signaling Pathway and the Treatment of Psoriasis. *J Immunol*. 2018;201(6):1605–1613. doi:10.4049/jimmunol.1800013
20. Furue K, Yamamura K, Tsuji G, et al. Highlighting interleukin-36 signalling in plaque psoriasis and pustular psoriasis. *Acta Derm Venereol*. 2018;98(1):5–13. doi:10.2340/00015555-2808
21. Johnston A, Xing X, Wolterink L, et al. IL-1 and IL-36 are dominant cytokines in generalized pustular psoriasis. *J Allergy Clin Immunol*. 2017;140(1):109–120. doi:10.1016/j.jaci.2016.08.056
22. Sugiura K, Takemoto A, Yamaguchi M, et al. The majority of generalized pustular psoriasis without psoriasis vulgaris is caused by deficiency of interleukin-36 receptor antagonist. *J Invest Dermatol*. 2013;133(11):2514–2521. doi:10.1038/jid.2013.230
23. Kanazawa N, Nakamura T, Mikita N, Furukawa F. Novel IL36RN mutation in a Japanese case of early onset generalized pustular psoriasis. *J Dermatol*. 2013;40(9):749–751. doi:10.1111/1346-8138.12227
24. Jordan CT, Cao L, Roberson ED, et al. Rare and common variants in CARD14, encoding an epidermal regulator of NF-kappaB, in psoriasis. *Am J Hum Genet*. 2012;90(5):796–808. doi:10.1016/j.ajhg.2012.03.013
25. Setta-Kaffetzi N, Simpson MA, Navarini AA, et al. APIS3 mutations are associated with pustular psoriasis and impaired Toll-like receptor 3 trafficking. *Am J Hum Genet*. 2014;94(5):790–797. doi:10.1016/j.ajhg.2014.04.005
26. Haskamp S, Bruns H, Hahn M, et al. Myeloperoxidase modulates inflammation in generalized pustular psoriasis and additional rare pustular skin diseases. *Am J Hum Genet*. 2020;107(3):527–538. doi:10.1016/j.ajhg.2020.07.001
27. Frey S, Sticht H, Wilschmann-Theis D, et al. Rare loss-of-function mutation in SERPINA3 in generalized pustular psoriasis. *J Invest Dermatol*. 2020;140(7):1451–1455.e1413. doi:10.1016/j.jid.2019.11.024
28. Capon F. A viewpoint on the genetic determinants of generalised pustular psoriasis. *Exper Dermatol*. 2023;32(8):1188–1193. doi:10.1111/exd.14746
29. Jordan CT, Cao L, Roberson ED, et al. PSORS2 is due to mutations in CARD14. *Am J Hum Genet*. 2012;90(5):784–795. doi:10.1016/j.ajhg.2012.03.012
30. Mahil SK, Twelves S, Farkas K, et al. APIS3 mutations cause skin autoinflammation by disrupting keratinocyte autophagy and up-regulating IL-36 production. *J Invest Dermatol*. 2016;136(11):2251–2259. doi:10.1016/j.jid.2016.06.618
31. Marrakchi S, Puig L. Pathophysiology of generalized pustular psoriasis. *Am J Clin Dermatol*. 2022;23(Suppl 1):13–19. doi:10.1007/s40257-021-00655-y
32. Twelves S, Mostafa A, Dand N, et al. Clinical and genetic differences between pustular psoriasis subtypes. *J Allergy Clin Immunol*. 2019;143(3):1021–1026. doi:10.1016/j.jaci.2018.06.038
33. Robinson A, Van Voorhees AS, Hsu S, et al. Treatment of pustular psoriasis: from the medical board of the national psoriasis foundation. *J Am Acad Dermatol*. 2012;67(2):279–288. doi:10.1016/j.jaad.2011.01.032
34. Miyachi H, Konishi T, Kumazawa R, et al. Treatments and outcomes of generalized pustular psoriasis: a cohort of 1516 patients in a nationwide inpatient database in Japan. *J Am Acad Dermatol*. 2022;86(6):1266–1274. doi:10.1016/j.jaad.2021.06.008
35. Bachelez H, Choon SE, Marrakchi S, et al. Trial of spesolimab for generalized pustular psoriasis. *N Engl J Med*. 2021;385(26):2431–2440. doi:10.1056/NEJMoa2111563
36. Burden AD. Spesolimab, an interleukin-36 receptor monoclonal antibody, for the treatment of generalized pustular psoriasis. *Expert Rev Clin Immunol*. 2023;19(5):473–481. doi:10.1080/1744666x.2023.2195165

37. Potestio L, Camela E, Cacciapuoti S, et al. Efficacy and safety of spesolimab for the management of generalized pustular psoriasis: a drug safety evaluation. *Expert Opin Drug Saf.* **2023**;1–8. doi:10.1080/14740338.2023.2265295
38. Hüffmeier U, Wätzold M, Mohr J, Schön MP, Mössner R. Successful therapy with anakinra in a patient with generalized pustular psoriasis carrying IL36RN mutations. *Br J Dermatol.* **2014**;170(1):202–204. doi:10.1111/bjd.12548
39. Imafuku S, Honma M, Okubo Y, et al. Efficacy and safety of secukinumab in patients with generalized pustular psoriasis: a 52-week analysis from Phase III open-label multicenter Japanese study. *J Dermatol.* **2016**;43(9):1011–1017. doi:10.1111/1346-8138.13306
40. Saeki H, Nakagawa H, Nakajo K, et al. Efficacy and safety of ixekizumab treatment for Japanese patients with moderate to severe plaque psoriasis, erythrodermic psoriasis and generalized pustular psoriasis: results from a 52-week, open-label, Phase 3 study (UNCOVER-J). *J Dermatol.* **2017**;44(4):355–362. doi:10.1111/1346-8138.13622
41. Yamasaki K, Nakagawa H, Kubo Y, Ootaki K. Efficacy and safety of brodalumab in patients with generalized pustular psoriasis and psoriatic erythroderma: results from a 52-week, open-label study. *Br J Dermatol.* **2017**;176(3):741–751. doi:10.1111/bjd.14702
42. Gargiulo L, Narcisi A, Ibba L, et al. Effectiveness and safety of bimekizumab for the treatment of plaque psoriasis: a real-life multicenter study-IL PSO (Italian landscape psoriasis). *Front Med.* **2023**;10:1243843. doi:10.3389/fmed.2023.1243843
43. Hagino T, Saeki H, Kanda N. Two cases of generalized pustular psoriasis successfully treated with bimekizumab. *J Dermatol.* **2023**;50(10):e357–e358. doi:10.1111/1346-8138.16866
44. Sano S, Kubo H, Morishima H, Goto R, Zheng R, Nakagawa H. Guselkumab, a human interleukin-23 monoclonal antibody in Japanese patients with generalized pustular psoriasis and erythrodermic psoriasis: efficacy and safety analyses of a 52-week, phase 3, multicenter, open-label study. *J Dermatol.* **2018**;45(5):529–539. doi:10.1111/1346-8138.14294
45. Pavia G, Gargiulo L, Spinelli F, et al. Generalized pustular psoriasis flare in a patient affected by plaque psoriasis after BNT162b2 mRNA COVID-19 vaccine, successfully treated with risankizumab. *J Eur Acad Dermatol Venereol.* **2022**;36(7):e502–e505. doi:10.1111/jdv.18032
46. Heyer S, Seiringer P, Eyerich S, et al. Acute generalized pustular psoriasis successfully treated with the IL-23p19 antibody risankizumab. *J Dtsch Dermatol Ges.* **2022**;20(10):1362–1364. doi:10.1111/ddg.14857
47. Arakawa A, Ruzicka T, Prinz JC. Therapeutic efficacy of interleukin 12/interleukin 23 blockade in generalized pustular psoriasis regardless of IL36RN mutation status. *JAMA Dermatol.* **2016**;152(7):825–828. doi:10.1001/jamadermatol.2016.0751
48. Matsumoto A, Komine M, Karakawa M, Kishimoto M, Ohtsuki M. Adalimumab administration after infliximab therapy is a successful treatment strategy for generalized pustular psoriasis. *J Dermatol.* **2017**;44(2):202–204. doi:10.1111/1346-8138.13632
49. Adachi A, Komine M, Hirano T, et al. Case of generalized pustular psoriasis exacerbated during pregnancy, successfully treated with infliximab. *J Dermatol.* **2016**;43(12):1439–1440. doi:10.1111/1346-8138.13429
50. Bachelez H, Choon SE, Marrakchi S, et al. Inhibition of the Interleukin-36 Pathway for the Treatment of Generalized Pustular Psoriasis. *N Engl J Med.* **2019**;380(10):981–983. doi:10.1056/NEJMc1811317
51. Onoufriadis A, Simpson MA, Pink AE, et al. Mutations in IL36RN/IL1F5 are associated with the severe episodic inflammatory skin disease known as generalized pustular psoriasis. *Am J Hum Genet.* **2011**;89(3):432–437. doi:10.1016/j.ajhg.2011.07.022

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