




Focuses and Trends of Research on Platelet-Rich Fibrin: A Bibliometric and Visual Analysis

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Abstract

Background A rapid expansion of study on platelet-rich fibrin (PRF) has gained more attention in the subject. In this study, bibliometrics were used to assess the outputs and trends of relevant PRF studies. An in-depth analysis of the publication patterns and progress in PRF research worldwide was conducted for the purpose of filling in this research gap.

Materials and Methods The analysis included 946 papers sourced from Web of Science that included 842 original articles and 104 reviews. A number of factors including country/region, institution, journal, and author were taken into account. Research on PRF development trends was mapped using the frequency of keywords.

Results In terms of the total number of publications, China ranked first with 199 papers, whereas the United States ranked first on the H-index with 37. PRF is an active research area in stomatology and craniomaxillofacial surgery. Keywords provided by the authors were designated to three clusters: red, green, and blue. "Growth factor," "platelet-rich plasma," and "bone regeneration" were the most frequent keywords in each cluster, which reflect the current interests in corresponding fields. Bone regeneration post-dental extractions is one of the main application directions in the field of oral and maxillofacial surgery. "Membrane," "injectable PRF (I-PRF)," "case report," and "advanced PRF (A-PRF)" were relative recent keywords in all clusters, indicating that manufacturing processes and new applications are promising research hotspots in the field.

Conclusion In the future, the applications of modified PRF, such as I-PRF, are promising research hotspots. Moreover, strict randomized controlled trials on PRF deserve more attention. The results of this analysis may be helpful for all scholars seeking to expand researches and innovations in the field of PRF.

Keywords

- ▶ bibliometric analysis
- ▶ platelet-rich fibrin
- ▶ growth factor
- ▶ bone regeneration
- ▶ membrane
- ▶ injectable

* These authors have contributed equally to this work and share first authorship.

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Introduction

Regeneration and engineering of tissues is a growing multidisciplinary field that aims to predictably format, enhance, or replace damaged tissues. Platelet concentrates acting as autologous biological blood-derived products are composed of plasma/platelet-derived bioactive components and fibrin-forming proteins, of which the components can create a natural three-dimensional structure. A concentrated pool of activated platelets can be used to deliver biomolecules to the injury site, which then functions in the modulation of inflammation, angiogenesis, and immune responses and facilitates wound healing.¹ Platelet concentrates are believed to be safe and clinically effective because of its autologous source and minimally invasive application procedure.² Platelet-rich plasma (PRP) is the main component of the first generation of platelet concentrates and is widely used in clinical work. Nevertheless, PRP has certain limitations, such as the need for exogenous additives, the short release of the bioactive components, and the lack of scaffold architecture.³ Platelet-rich fibrin (PRF) serves as one of the second generation products of platelet concentrates and represents the most popular one, it facilitates an enhanced healing process via releasing cytokines from a three-dimensional fibrin matrix of PRF.⁴ Over the years, PRF has become an exciting and new area of tissue regeneration and engineering research.

Bibliometrics analysis, a quantitative analysis approach that uses statistical and mathematical equations to measure the interrelationships and impact of publications within a given area of research, has become increasingly popular in the last few years. Compared to the traditional counting of citations, bibliometrics considers the links between articles; in particular, it identifies emerging trends and intellectual structures. In this study, research trends and scientific outputs of PRF studies were assessed using bibliometrics.

Materials and Methods

Data Sources and Search Strategies

The Web of Science Core Collection (WoSCC) database, a credible database for bibliometric analysis, was used to conduct a comprehensive online search for PRF research. The articles were downloaded in plaintext form in order to analyze the data. This study did not require ethical consent since the data was obtained from a public database and did not include human subjects.

A one-day (March 17, 2022) search was conducted in order to prevent inconsistencies caused by the rapid database renewals. Search strategies were developed to reduce the inclusion of articles with insufficient relevance while incorporating as many relevant articles as possible: TI=(“platelet rich fibrin”) or AK=(“platelet rich fibrin”) AND language=English. TI represents “title” and AK represents “author keywords.” Importantly, original articles and reviews appearing in the Science Citation Index Expanded were included. Two researchers (Y.Z. and C.D.) independently formulated and negotiated the initial search strategies. The

senior researcher (S.H.) resolved the existing disputes and finally determined the search strategies.

Data Collection

Based on correlative publications, two authors (Y.Z. and C.D.) independently extracted keywords, publication dates, origin countries, authors, institutions, journals, citations, etc. GraphPad Prism 9 and VOSviewer 1.6.18 were used to analyze the WoSCC data quantitatively and qualitatively.

Bibliometric Analyses

Bibliographic data composed of publication numbers, publication countries/regions, name of journals, institutions, authors, keywords, and citations were analyzed. For the research scope of PRF, the calculations were made as follows: (1) the contributions of countries/regions to global publications, including the number of publications, quantity of citations, value of H-index, and country/region-wise coauthorship; (2) the different publication distributions of distinct journals; (3) the frequency of coauthorship between different institutions and institution-by-institution; (4) the authors who published the most publications, with the most cited papers and author-wise coauthorship; (5) clusters and emergence time of keywords; and (6) network of direct and cocitations of published papers.

An analysis of the publication characteristics was conducted using a statistical tool in the Web of Science. Then, VOSviewer was applied to create the collaborative map using the information comprising of countries/regions, institutions, and authors. Across the created map, the size of a circle represented the quantity of publications, while the width of a line indicated the magnitude of a collaboration. Color-matched items were in the same cluster, indicating close cooperation.

Results

Growth Trend of Publications

According to our screening criteria, 946 publications met our criteria, including 842 articles (89%) and 104 reviews (11%). Globally, publications of PRF have increased significantly over time. Two articles were published on PRF in 2006 and 167 in 2021. Because original articles and reviews are the two most representative publications, we limited search strategies within original articles and reviews, and excluded other types of publications such as meetings, abstracts, and letters. According to your suggestions, we have manually judged the 946 publications one by one. According to the analysis, there are 70 randomized controlled trials (RCTs), 60 case reports/series, and 32 meta-analyses. A total of 842 articles refer to the original papers. No matter what kind of articles, the publishing trend is consistent with the general trend. With the passage of time, the publication number has increased greatly, which shows that PRF is the current research hotspot.

Bibliometric Analysis of Countries/Regions

With reference to the number of publications, China ranked first with 199 (21.0%), followed by Turkey with 138 (14.6%)

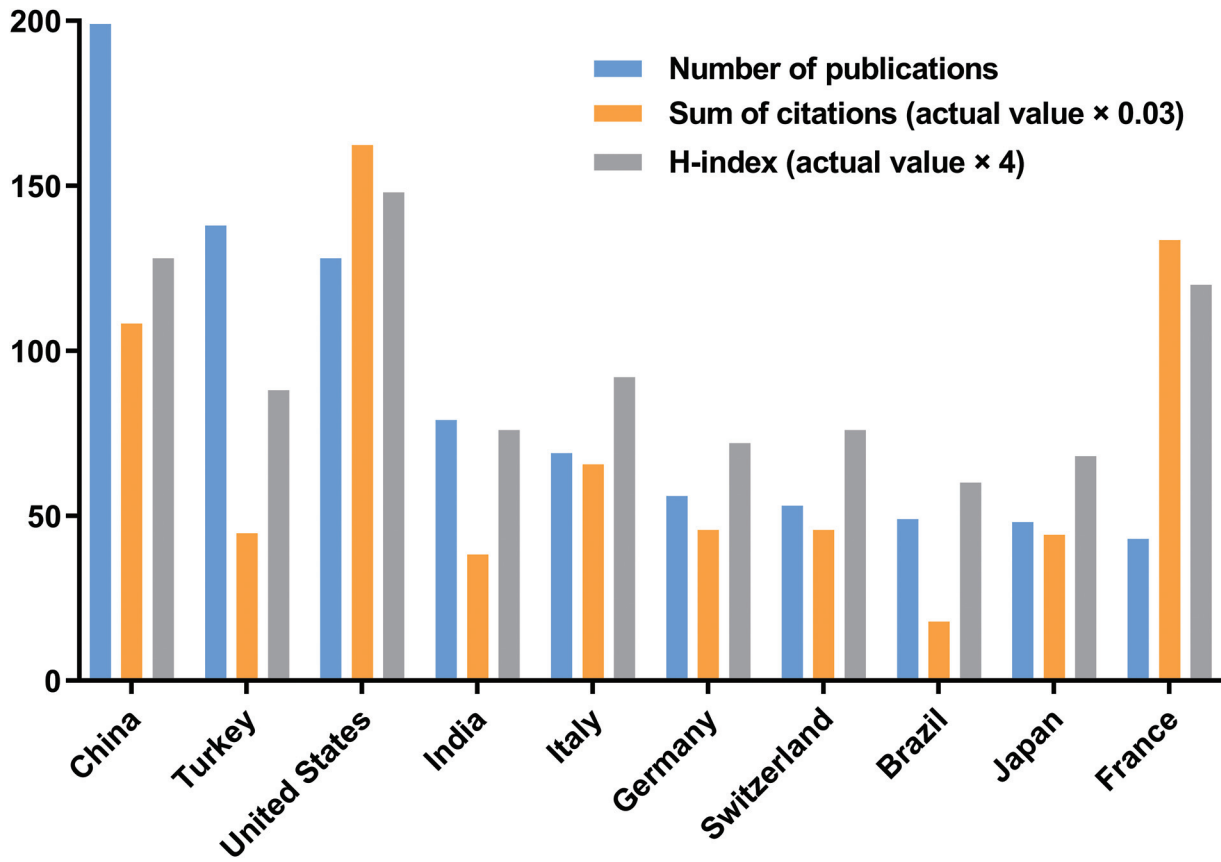


Fig. 1 Number of publications in the research field of platelet-rich fibrin.

and the United States with 128 publications (13.5%, ► Fig. 1). Nevertheless, the United States ranked first on the H-index (37). Notably, France, the birthplace of PRF, did not have the most articles; however, its H-index (30) and citations (4,450) are among the highest.

Bibliometric Analysis of Journals and Institutions

According to ► Fig. 2, these are the top 10 journals with the most publications, mainly focused on stomatology and craniomaxillofacial surgery. The highest number of papers was published by the *Journal of Periodontology* (40 publications; 4.2%). As for institutions focusing on PRF, the League of European Research Universities published the most papers (62, 6.6%).

Bibliometric Analysis of Authors

As shown in ► Table 1, the top nine authors have published the most studies on PRF. The largest number of papers was published by Miron (42 papers). Notably, Ehrenfest, Choukroun, and Miron were the top three authors in the field (with the highest citation frequency).

Bibliometric Analysis of Keywords

According to ► Fig. 3, 71 keywords that occurred more than six times were identified and classified into three clusters: red, green, and blue. In the red cluster, “growth factor,” “wound healing,” and “tissue regeneration” were the top three search terms. In the green cluster, “platelet-rich plasma,” “platelet,” and “fibrin” were the most frequently

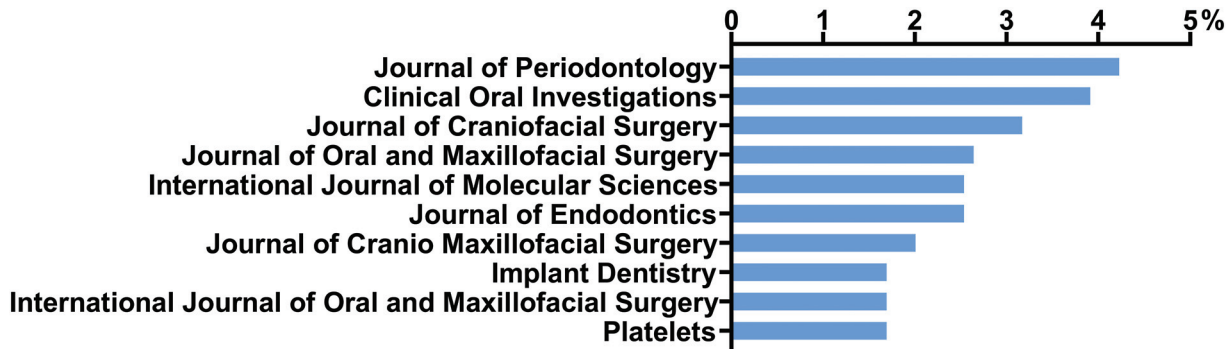


Fig. 2 The top 10 journals that publish studies on platelet-rich fibrin.

Table 1 Top nine authors with most publications in research scope of platelet-rich fibrin

Author	Country ^a	Affiliation ^a	Publications (n)	Citations (n)
Miron	Switzerland	University of Bern	42	1,399
Zhang	China	Wuhan University	29	1,029
Ghanaati	Germany	The Goethe University Frankfurt	25	983
Choukroun	France	Pain Clinic Center	22	2,413
Kawase	Japan	Niigata University	20	368
Ehrenfest	Sweden	University of Gothenburg	19	2,863
Quiryne	Belgium	University Hospitals Leuven	19	589
Zhou	China	Jilin University	18	159
Gruber	Austria	Medical University of Vienna	17	200

^aCitations are based on the most recent or highest cited publication.

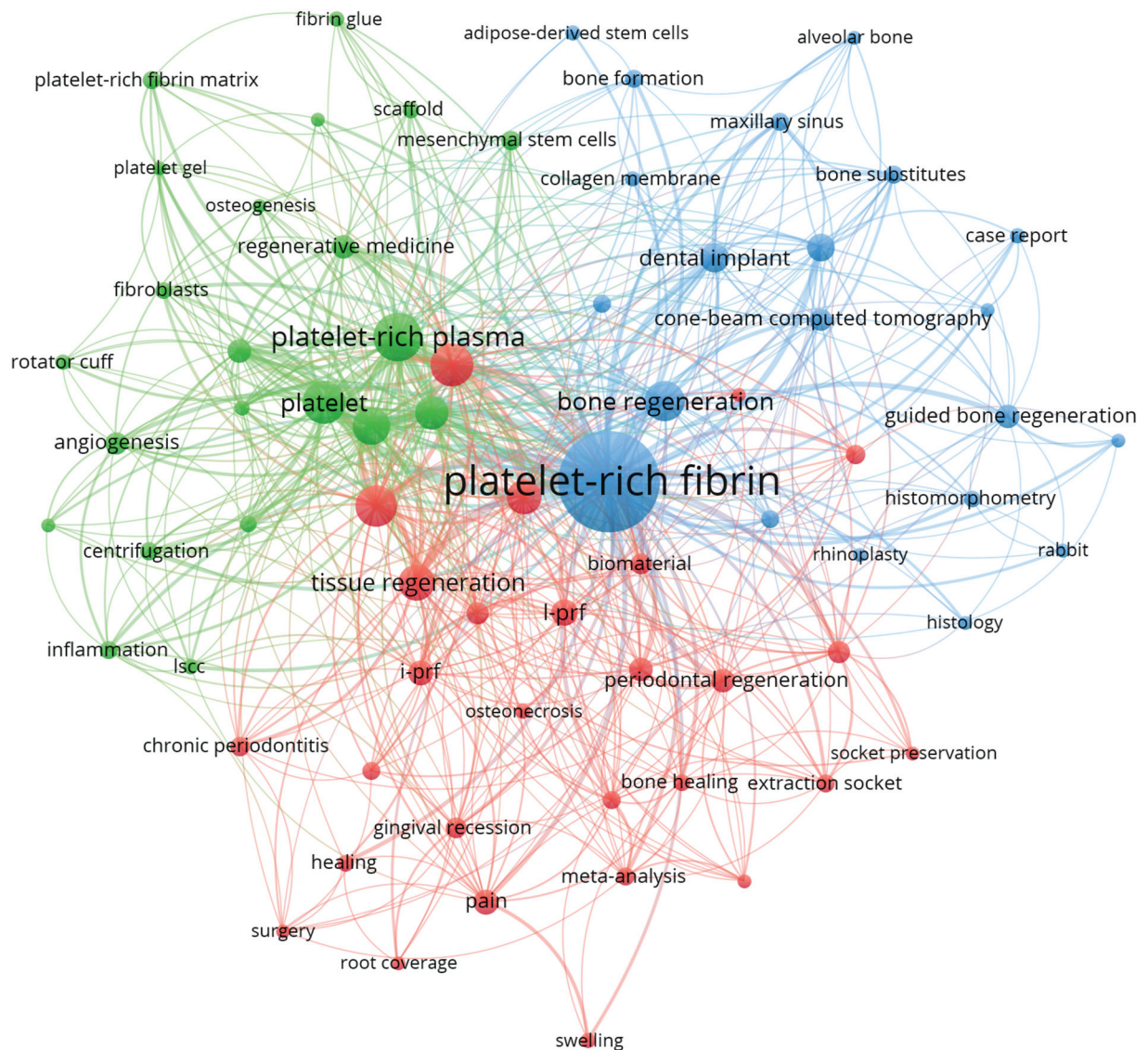


Fig. 3 Keyword map for platelet-rich fibrin. Various colors indicate three clusters of keywords. Keywords with high frequency are indicated by a large icon.

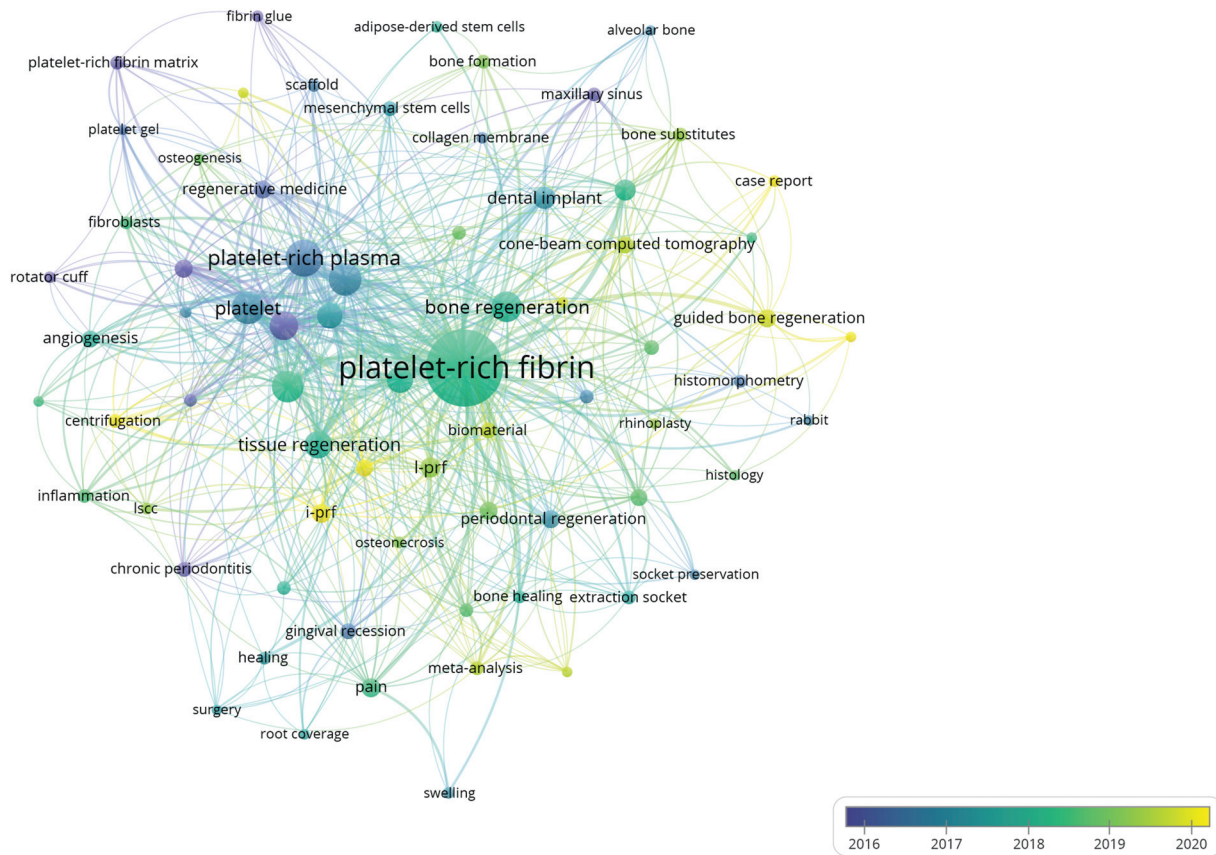


Fig. 4 Based on the average appearance date, the distribution of keywords is displayed in blue for early appearances and yellow for recent appearances.

searched terms. In the blue cluster, besides PRF itself, the top three keywords were “bone regeneration,” “dental implant,” and “sinus floor elevation.” In **Fig. 4**, keywords were colored according to their average publication years (APY); specifically, blue indicates that the keyword was published a long time ago, while yellow indicates that it was published recently (Xia et al, 2021⁵). For example, early in history, the APY for “fibrin glue” was 2012.10, whereas “centrifugation” is a relatively new keyword with an APY of 2019.9. “Membrane,” “injectable PRF (I-PRF),” “case report,” and “advanced PRF (A-PRF)” were the relatively recent keywords in all clusters. The cooccurrence results of all keywords are showed in **Supplementary Table S1**, available in the online version.

Bibliometric Analysis of Citations

PRF-related publications in this study were cited 19,611 times in total, with an average citation frequency of 20.7 times. The top nine highly cited articles related to PRF are shown in **Table 2**.

Discussion

Since the turn of the century, papers reporting on PRF have been gradually increasing, suggesting its importance as a research hotspot. We found that China is the most active country in the field, and Zhang and Zhou have been two of the most productive and active researchers. In regard to the total citations and H-index, the United States stands for the

most influential country with respect to PRF research. Furthermore, Europe is an active region for PRF studies, both institutionally and by authors.

Research Focuses

Apart from PRF’s keywords, the keywords revealed the following focus areas.

“Growth factor” was the most frequent keyword in the red cluster. PRF is rich in many growth factors, which are key molecules for regulating inflammation and promoting wound healing, such as platelet-derived growth factor (PDGF), transforming growth factor-β, and insulin-like growth factor 1.⁶ In addition, the PRF in the wound bed can spontaneously form a dense fibrin complex, which endows PRF with the potential of slower degradation, thus delaying the release of growth factors to the surrounding tissues.⁷ The time of growth factors releasing from PRF can last for up to 7 days for most of them, while certain ones can last for even longer.^{8,9} As a result, PRF harbors the advantage of longer releasing time of growth factors in contrast to other platelet concentrates.

“PRP” was the most frequently seen keyword in the green cluster. PRF is considered a second-generation platelet concentrate, so its comparison with PRP, a representative of first-generation platelet concentrate, has always been the focus of PRF research. Compared to PRP, PRF has the following advantages: (1) blood prepared for PRF is collected without any anticoagulant and needs only to be centrifuged once,¹⁰ (2) the fibrin in PRF provides scaffolding for clots and helps

Table 2 Top 9 high cited articles related to platelet-rich fibrin

Title	Journal	Publication year	Total citations (n)	Average citations per year (n)
Platelet-rich fibrin (PRF): A second-generation platelet concentrate. Part V: Histologic evaluations of PRF effects on bone allograft maturation in sinus lift	<i>Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology</i>	2006	1,019	1,019
Classification of platelet concentrates: from pure platelet-rich plasma (P-PRP) to leucocyte- and platelet-rich fibrin (L-PRF)	<i>Trends in Biotechnology</i>	2009	873	873
Comparison of surgically repaired Achilles tendon tears using platelet-rich fibrin matrices	<i>American Journal of Sports Medicine</i>	2007	399	399
New insights into and novel applications for platelet-rich fibrin therapies	<i>Trends in Biotechnology</i>	2006	340	340
Slow release of growth factors and thrombospondin-1 in Choukroun's platelet-rich fibrin (PRF): a gold standard to achieve for all surgical platelet concentrates technologies	<i>Growth Factors</i>	2009	281	281
A comparative study of platelet-rich fibrin (PRF) and platelet-rich plasma (PRP) on the effect of proliferation and differentiation of rat osteoblasts in vitro	<i>Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology</i>	2009	271	271
Comparative release of growth factors from PRP, PRF, and advanced-PRF	<i>Clinical Oral Investigations</i>	2016	238	238
Three-dimensional architecture and cell composition of a Choukroun's platelet-rich fibrin clot and membrane	<i>Journal of Periodontology</i>	2010	222	222
The clinical use of human culture-expanded autologous bone marrow mesenchymal stem cells transplanted on platelet-rich fibrin glue in the treatment of articular cartilage defects: A pilot study and preliminary results	<i>Cartilage</i>	2010	219	219

mesenchymal stem cells to become localized,¹¹ and (3) PRF including compatible, or higher levels of platelets and PDGFs may facilitate cell proliferation without side effects at a higher dose.¹² These properties make PRF, an autologous biomaterial, be widely used in regenerative medicine and tissue engineering.

"Bone regeneration" was the most frequent keyword in the blue cluster. PRF promotes bone regeneration, for instance, of bone defect after tumor surgery, periapical bone destruction resulted from periapical periodontitis, and alveolar bone atrophy.¹³ In vitro studies showed that alkaline phosphatase activity, calcification, and mineralization gradually increase in osteocytes treated with PRF.¹⁴ In vivo studies further showed that PRF is superior in promoting soft tissue healing and hastens bone formation in extraction sockets.¹⁵ The most important reason for using PRF to accelerate bone regeneration is to release growth factors from platelets' alpha granules.¹⁶ Besides, PRF provides a three-dimensional microenvironment to facilitate osteogenesis.¹⁷ In addition to bone regeneration, researchers have provided supporting evidence in such fields as gingival

recession, dental implants stability, temporomandibular joint osteoarthritis, etc. in the field of oral and maxillofacial surgery.

Research Trends

In this study, "membrane," "I-PRF," "A-PRF," and "case report" were found to be the newest keywords showing the representative trends of PRF research.

Recent studies showed some new clinical applications for PRF membranes. Due to the plasticity of PRF clots, PRF can be easily pressed into a membrane shape.¹⁸ Swarnakar et al. successfully cured a patient with a pressure ulcer caused by spinal cord injury using a PRF membrane.¹⁹ Animal models further proved that PRF membranes could assist nerve and cartilage tissue regeneration.^{20,21} PRF membrane has also been perceived as a safe, effective, and promising method to prevent pterygium recurrence after surgery.²² Furthermore, different preparation processes can also have subtle effects on the physicochemical properties of PRF membranes. Wei et al. evaluated the effect of resting and compression time postcentrifugation on the characteristics of PRF membranes

and revealed that PRF membranes showed maximum weight, volume, and mechanical properties after resting for 3 to 5 minutes in the tube postcentrifugation followed by a compression time of 120 seconds.²³

Initially, PRF was called leucocyte- and PRF, which is obtained as a clot after centrifugation at 408 g relative centrifugal force (RCF) for 12 minutes.²⁴ In 2014, Ghanaati et al. proposed a new protocol to produce A-PRF, which decreases speed and increases the time of centrifugation (RCF: 193 g, for 14 minutes).²⁵ Previous studies suggested that reducing RCF may increase the release of growth factors and the concentration of leucocytes and platelets.²⁶ However, a recent comparative study showed that adaptation of RCF only had a minimal impact on the final characteristics of PRF.²⁷ I-PRF is a flowable PRF formulated by centrifugation at lower speeds for only 3 minutes.²⁸ Based on these described above, clinicians now have access to an easy-to-use I-PRF in liquid form, which can be used alone or combined with different kinds of biomaterials.²⁹

PRF has been mainly used in oral and maxillofacial surgery; yet, more recently, its application has gradually expanded to plastic surgery, dermatology, and other wider fields. Some forward-looking scholars have made reasonable attempts on individual cases. Pires et al. reported the successful application of PRF in the treatment of patients suffering from endodontic microsurgery of the upper lateral incisors with loss of buccal cortical plate.³⁰ Bansod cured a patient with a large wound defect resulted from severe irritant contact dermatitis due to slaked lime using PRF therapy in combination with high-dose oral vitamin C.¹ Moreover, the application of PRF in promoting osteoanaphysis has also been extended to nonmaxillofacial bone, such as tibiofibular.³¹ According to the results of bibliometric analysis and our perspectives, the future research trends of PRF may include the following: (1) PRF manufacturing process needs to be deeply studied and continually optimized, including in combination with other materials or drugs; (2) effects of different states of blood donors on PRF need to be further investigated; (3) the mechanism of PRF inducing tissue regeneration deserves further elucidation; (4) except oral and maxillofacial surgery, the clinical application of PRF needs to be further explored; and (5) strict RCTs are necessary to provide evidence-based evidence for the use of PRFs.

Conclusion

This study used bibliometric analysis to determine how PRF research has progressed. The number of publications on PRF has significantly increased over the years, and China has been the most productive country. Going forward, the application of modified PRF for tissue regeneration, such as bone regeneration, might represent promising research hotspots; moreover, further strict RCTs are required on the topic. However, we have to acknowledge that many research articles published not in English and numerous unpublished researches were not included in this article, their contributions to PRF research should also be considered.

Authors' Contributions

Y.Z. and C.D. drafted, proofread the manuscript, and prepared the figures. S.H. and Z.Y. edited the manuscript. X.G., T.L., and L.F. revised the manuscript. All authors have agreed upon the submission and publication of this work. Y.Z. and C.D. contribute equally to this review and should be considered cofirst authors.

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Conflict of Interest

None declared.

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