



RESEARCH ARTICLE

Research Status and Hotspots of Chronic Osteomyelitis: A Bibliometric and Visualized Analysis

Jinlun Chen, MD^{1,2}, Xingyu Wang, MM³, Jin Li, MM⁴, Haitao Zhang, MD², Yijin Li, MM², Peng Deng, MD¹, Wenjun Feng, MD¹ , Xinyu Qi, MD¹, Pengcheng Ye, MM¹, Jiahao Li, MM², Jianchun Zeng, MD¹, Yirong Zeng, MD¹, Jie Li, MD¹ , Shuihua Xie, BM³

¹The Three Department of Orthopedics, The First Affiliated Hospital of Guangzhou University of Chinese Medicine and ²The First Clinical Medical College, Guangzhou University of Chinese Medicine, Guangzhou, ³The First Department of Orthopedics, Jiangxi Province Hospital of Integrated Chinese and Western Medicine, Nanchang and ⁴The Fourth Clinical Medical College, Guangzhou University of Chinese Medicine, Shenzhen, China

Objective: The treatment of chronic osteomyelitis (COM) is extremely challenging for physicians and patients. It is of great significance to explore the research status, development trend and future research hotspots in the field of COM to promote the development of this field. This study is aimed to explore the global research status of COM and predict its future research hotspots based on bibliometric and visualized analysis.

Methods: Web of Science core collection database was used to search the related literature of COM from 1994 to 2020. All data were imported into Microsoft Excel 2019 for collation. Additionally, the literature quality of countries, authors, journals, and institutions is evaluated. The VOS viewer software was used for conducting co-analysis, co-citation analysis, and keyword co-occurrence analysis of literature to analyze the global status and predict the future hotspots of the COM field.

Results: A total of 726 articles were retrieved in this study. The number of global publications shows a trend of wave growth, but the increase is not significant. It is expected that the number of COM articles will remain at more than 50 per year in the next decade. The COM literature published in the United States (Publications = 160, H index = 37, average citations per item = 28.63) is of the highest quality. Girschick HJ (Publications = 16, H index = 14, average citations per item = 52.25) is the most contributed scholar in the field of COM. UNIV IOWA (Publications = 15, H index = 11, average citations per item = 57.27) and UNIV WURZBURG (Publications = 18, H index = 15, average citations per item = 47.5) are influential institutions in the field of COM. The results of co-occurrence analysis show that the field of COM can be roughly divided into the following five modules: COM surgical research, COM basic research, COM diagnosis-related research, chronic recurrent multifocal osteomyelitis (CRMO)-related research, risk factors of COM. Risk factors of COM are the module with the highest concentration of hot words.

Conclusion: COM-related research will continue to develop further in the next decade. The diagnosis research and risk factors of COM are the most popular research modules in recent years. Some controversial or troubled issues including the efficacy of perforator flap and fascia flap covering soft tissue, searching exclusive detection methods for the diagnosis of COM and bisphosphonates and biological agents in the treatment of CRMO may lead to the development of the COM field.

Key words: chronic osteomyelitis; future hotspot; research status; visualization

Address for correspondence Yirong Zeng, The Three Department of Orthopedics, The First Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou 510405, Guangdong, China. Email: zeng1966zeng@126.com; Shuihua Xie, The First Department of Orthopedics, Jiangxi Province Hospital of Integrated Chinese and Western Medicine, No.90, Bayi Road, Xihu District, Nanchang 330003, Jiangxi, China, Email: xieshuihua6601@163.com. Jinlun Chen and Xingyu Wang contributed equally to this work and are considered co-first authors.

Received 27 July 2021; accepted 23 August 2022

Introduction

Chronic osteomyelitis (COM) is a chronic disease of bone marrow, periosteum, bone cortex, and surrounding tissue necrosis caused by pathogenic bacteria or aseptic inflammation.^{1,2} COM resulting from a variety of causes, including host tissue necrosis, post-traumatic acute osteomyelitis, diabetic foot, internal fixation surgical infection, and blood dissemination.³ Accurate diagnosis of COM is the fundamental key to successful treatment. However, the atypical symptoms of early COM and the lack of precise laboratory markers and imaging scans make its diagnosis difficult.^{4,5} In addition, pathogens can easily avoid antibiotics and develop drug resistance because they can form biofilms on the surface of bone or implants.⁶ Hence, the treatment of COM is extremely challenging for both doctors and patients due to its long treatment cycle, high recurrence rate, and high disability rate. At present, a number of studies have systematically reviewed the research progress in the sub-field of COM. A meta-analysis by Qi *et al.* showed that the total radical cure rate of COM treated with antibiotics-calcium sulfate was 92%.⁷ Arshad *et al.* concluded that the treatment principles of COM are removal of infected tissue, dead space management, and antibiotic treatment.⁸ Bury believes that magnetic resonance imaging with and without contrast agents is more sensitive for identifying late osteonecrosis areas.⁹ Nevertheless, the global research trend and future hotspots prediction in this field are rarely systematically studied. Against this background, it is of great significance to explore the research status, development trend, and future research hotspots in the field of COM to promote the development of this field and lead scholars to overcome clinical difficulties in a targeted direction.

As an emerging means, bibliometrics help researchers to qualitatively and quantitatively grasp the scientific output and research trend in a certain research field in a short time.¹⁰ It mainly concentrates on the analysis of the contributions of research institutions, researchers or groups, journals, and countries to a certain field. The information displayed by bibliometrics is more intuitionistic and abundant combined with visual analysis. To date, bibliometrics have been used in many medical research domains, such as subchondral bone, cesarean section scar uterine pregnancy, acupuncture treatment of insomnia, osteoporosis.¹¹⁻¹⁵ Therefore, this study aims to use bibliometrics and visualization to (i) evaluate the research status and development trend of COM since the Web of Science Core Collection (WOSCC) database was established and (ii) to predict research hotspots of COM over the next few years. We hypothesize that the research on COM will increase year by year. The research focus of COM is mainly focused on early diagnosis and radical cure.

Methods

Data Sources and Retrieval Strategies

Publications retrieval was completed by two independent authors (Chen JL and Zhang HT). The inclusion criteria are

as follows: (i) original articles and review article on COM from 1994 to 2020; (ii) English literature; (iii) the literature is from the WOSCC database. The exclusion criteria are as follows: (i) other types such as conference papers, only abstracted literature, newspaper articles, protocol, and patents. The search term was as follows: TI = (chronic osteomyelitis), language (English), literature type (Article or review) index = SCI-EXPANDED time = 1994-2020. The literature search period ended on March 1, 2021.

Data Extraction Content

Download all the records determined by the retrieval strategy and extract the data. Data extraction content is as follows: (i) year, country, author, affiliated institution, journal name, keywords, abstract of the publication; (ii) H index, average cited frequency of each item, total cited frequency of countries, authors, institutions and journals; (iii) the top 10 cited literature titles, year of publication, main research conclusions, source journals (impact factors). Impact factors are obtained from the 2019 version of the Journal Citation Reports. The data are downloaded through the functions of "creating citation report" and "analyzing retrieval results," respectively. The format of the downloaded file is "TXT," and the contents are fully recorded and cited references.

Statistical Analysis and Visualization

All data were imported into Microsoft Excel 2019 for collation. Microsoft Excel was used to perform a broken-line trend chart of the number of documents published each year, and a combination map of publications quality evaluation of countries (or regions), authors, journals, and institutions. The blue trend line in the broken-line trend chart represents the overall literature publication trend, which is completed by the linear trend line function in Microsoft Excel 2019. GraphPad Prism 8.0 (San Diego, USA, GraphPad Software) was used to draw pie charts of the top 10 countries (regions), authors, journals, and institutions. The "TXT" files containing fully recorded and cited references were introduced into VOSviewer version 1.6.15 (Van Eck and Waltman, Leiden University, Leiden, The Netherlands) for co-authorship analysis and co-occurrence analysis. Co-occurrence analysis included a clustering visualization map and hotspot prediction visualization map.

Results

Literature Quantity and Growth Trend

A total of 726 articles related to COM were included. Among them, there are 90 (12.4%) prospective clinical studies, 356 (49.0%) retrospective clinical studies, 98 (13.5%) basic studies, and some secondary studies such as systematic review and meta-analysis. Figure 1 shows that the number of global publications presents a trend of wavy growth, but the increase is not significant. In the past 4 years, the number of publications has exceeded 40. The year 2020 ($n = 52$) is currently the year with the largest number of articles published.

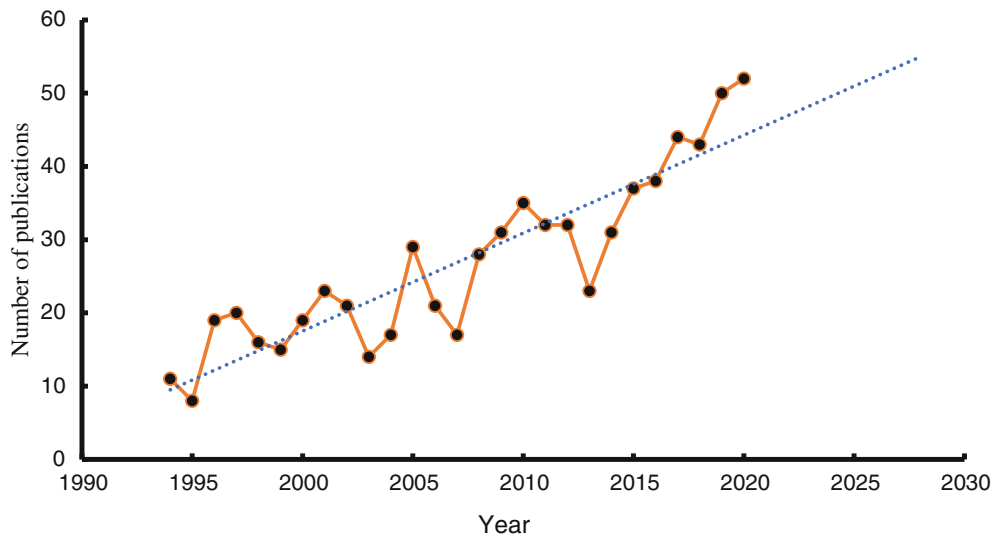


Fig. 1 Growth trend curve of the cumulative number of global chronic osteomyelitis (COM) publications

The blue trend prediction line suggests that the number of publications in the next decade will remain at more than 50.

Country (Region) Distribution, Quality Evaluation, and Co-Author Analysis

A total of 62 countries around the world have participated in the study of COM. The top 10 countries (regions) with the largest number of publications are shown in Figure 2A. The United States ($n = 160$, accounting for 22.03%) is the country with the largest number of published literatures in this field, followed by Germany ($n = 81$, accounting for 11.16%) and China ($n = 75$, accounting for 10.33%). H index and cited frequency are usually used as indicators of contribution among comparative scholars. H index and cited frequency are usually used to measure the contribution among scholars. Concerning the literature quality assessment of countries (regions), the United States has the highest H index (37), Germany's H index (33) ranks second, but other countries are almost at the same low level. As for the average cited frequency per item, Germany is the highest (37.52), France, which ranks ninth in the number of publications, ranks second (29.92), and the United States ranks third (28.63) (Figure 2B). The total cited frequency of the United States (4581) and Germany (3039) far exceeded other countries, ranking first and second, respectively. In the co-authoring visualization analysis of countries (regions), the United States has the largest node, with 16 connecting lines and total links strength (TLS) of 240, followed by Germany, which has cooperative relations with 14 countries (TLS = 105) (regions).

Institutions Distribution, Literature Quality Evaluation, and Co-Author Analysis

Figure 3A shows the top 10 subordinate organizations. CHINA MED UNIV ($n = 21$) ranked first. CHINA MED UNIV HOSP ($n = 20$) and UNIV WURZBURG ($n = 18$) ranked second and third, respectively. The first two

institutions come from China. However, their literature quality seems mediocre. UNIV WURZBURG¹⁵ H index ranks first (Figure 3B). The UNIV IOWA of the United States ranks first in the average cited frequency per item and total cited frequency. In the co-visualization analysis of institutions, Univ Wurzburg (TLS = 19) and Univ Iowa (TLS = 16) collaborated with eight and seven institutions, respectively (Figure 3C).

Author Distribution, Literature Quality Assessment, and Co-Citation Analysis

The top 10 authors were shown in Figure 4A. Girschick HJ ($n = 16$) and Tseng CH ($n = 16$) were the two authors with the most published literature in the field of COM. Besides, Girschick HJ ranked first in three indicators of literature quality evaluation, with 14, 52.25 and 820 respectively (Figure 4B). In the co-citation analysis of authors, Girschick HJ (links = 85, TLS = 4310) is the most co-cited of all authors and has the strongest correlation with other authors (Figure 4C).

Journal Distribution, Literature Quality Assessment, and Co-Citation Analysis

Among the top 10 published journals, *International Orthopedics* ($n = 15$) has published the greatest number of COM-related literatures. By comparison, *Clinical Orthopedics and Related Research* is a high-quality journal recognized by scholars, with a H index, average cited frequency, and total cited frequency of 10, 31.17, and 374, respectively. Consistent with the quality of the literature, the co-citation analysis of journals showed that *Clinical Orthopedics and Related Research* had the highest links (links = 168, TLS = 101,298) (Figure 5).

Top 10 countries (regions)

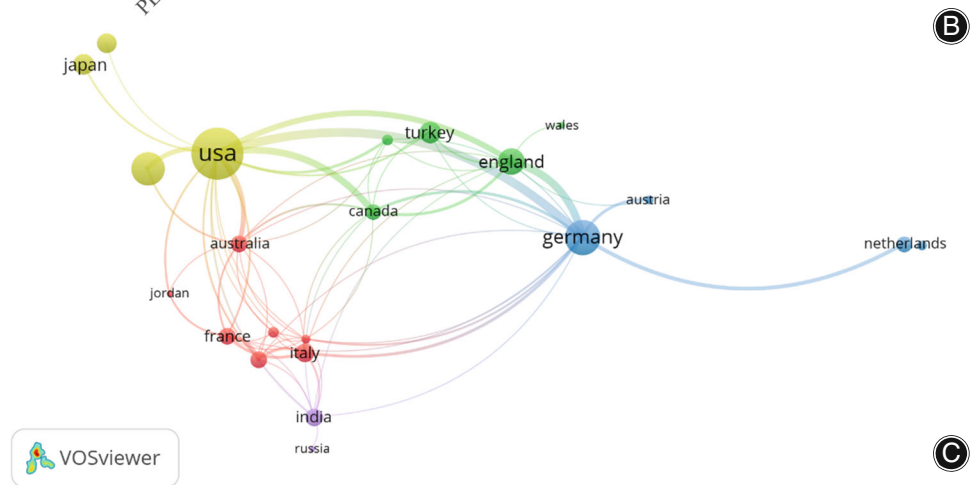
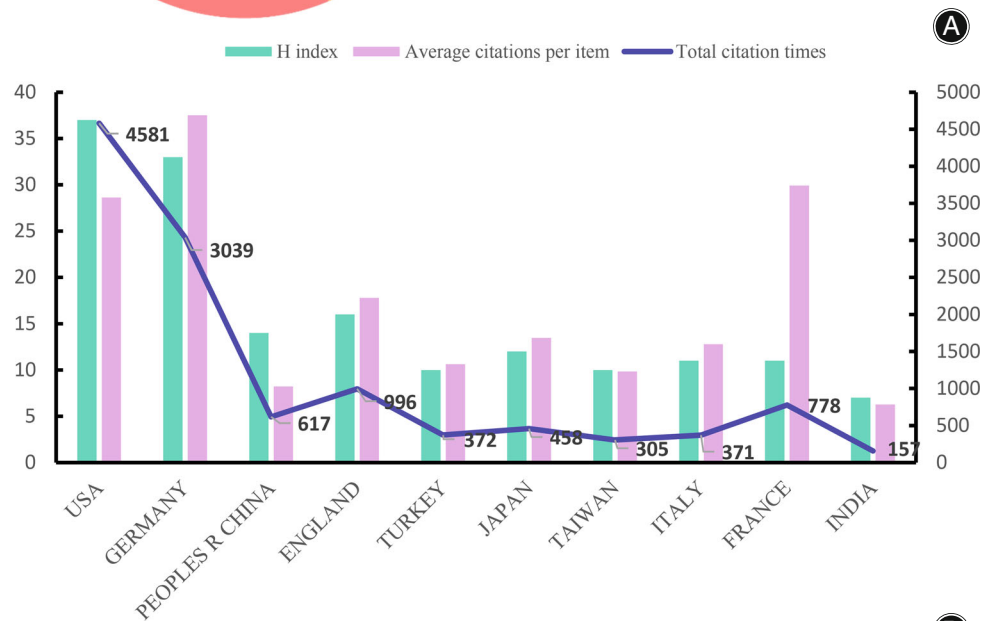
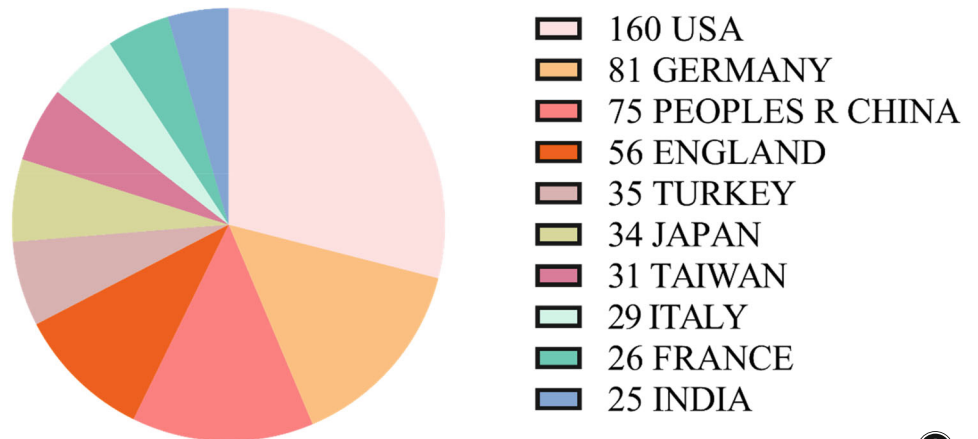
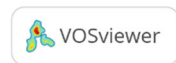


Fig. 2 (A) Top 10 countries (regions) of publications number. (B) Country (region) literature quality index. (C) Co-author analysis of the country



Top 10 Cited Pieces of Literature in the Field of COM
Table 1 displayed the top 10 citations in the COM field. The influence factors of 10 articles were all higher than

3 points. Nine pieces of literature were published before 2010, and only “Systemic Antibiotic Therapy for Chronic Osteomyelitis in Adults” was published in 2012. There are

Top 10 institutions

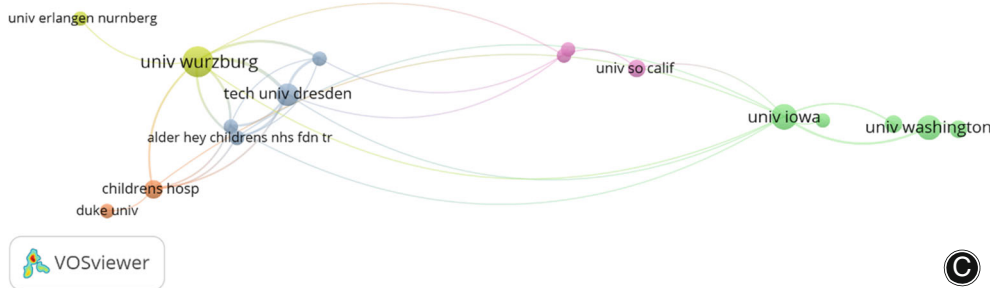
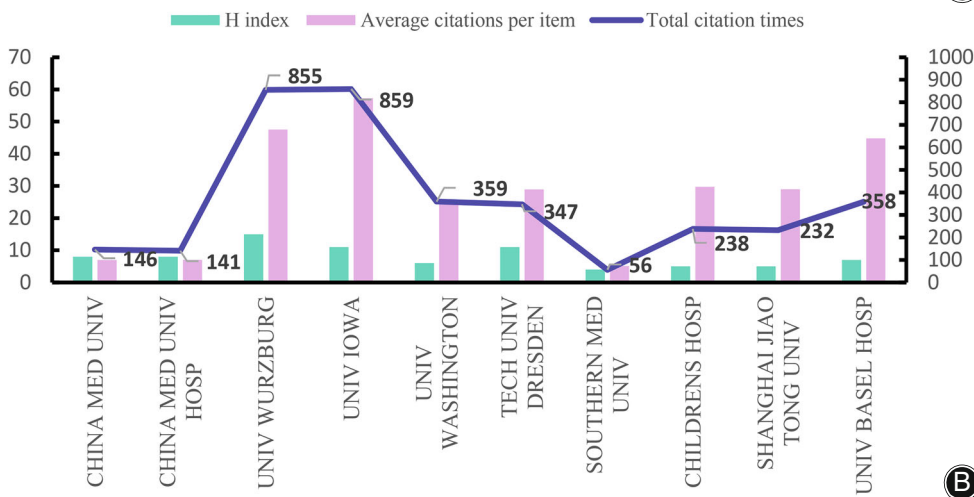
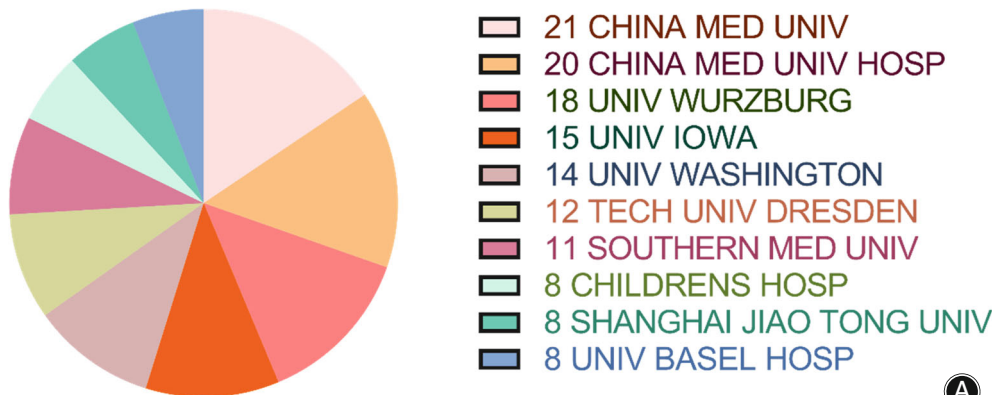


Fig. 3 (A) Top 10 institutions of publications number. (B) Institutions literature quality index. (C) Co-author analysis of the institution

three articles about the diagnosis of COM and three articles about CRMO.

Co-Occurrence Analysis

In the co-occurrence analysis of keywords, set the minimum repetition frequency to five times, a total of 801 keywords met the standard, and finally 481 keywords are presented in Figure 6. The COM domain can be roughly divided into five modules: COM surgical research, COM basic research, COM diagnosis-related research, chronic recurrent multifocal osteomyelitis (CRMO)-related research, COM-related risk factors (Figure 6A). The keywords with the highest frequency in module 1 are as follows: debridement, wound, surgical treatment,

bone defect, healing, muscle flap, reconstruction. The most common keywords in module 2 are as follows: *Staphylococcus aureus*, vancomycin, animal, methicillin-resistant *S. aureus*, strain, bacterial load, *in vitro*. The more frequent keywords in module 3 are as follows: sensitivity, specificity, accuracy, positive likelihood ratio, fluorodeoxyglucose-positron emission tomography (FDG-PET). The most striking keywords in module 4 are as follows: chronic recurrent multifocal osteomyelitis, chronic nonbacterial osteomyelitis, children, adolescents, syndrome, bisphosphates. The keywords with the highest frequency in module 5 are as follows: age, risk factors, population, sex, complications, diabetes. Figure 6B indicated that each module distributes more or less hot keywords, but

Top 10 authors

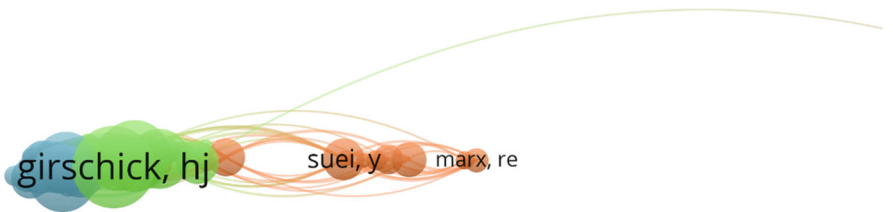
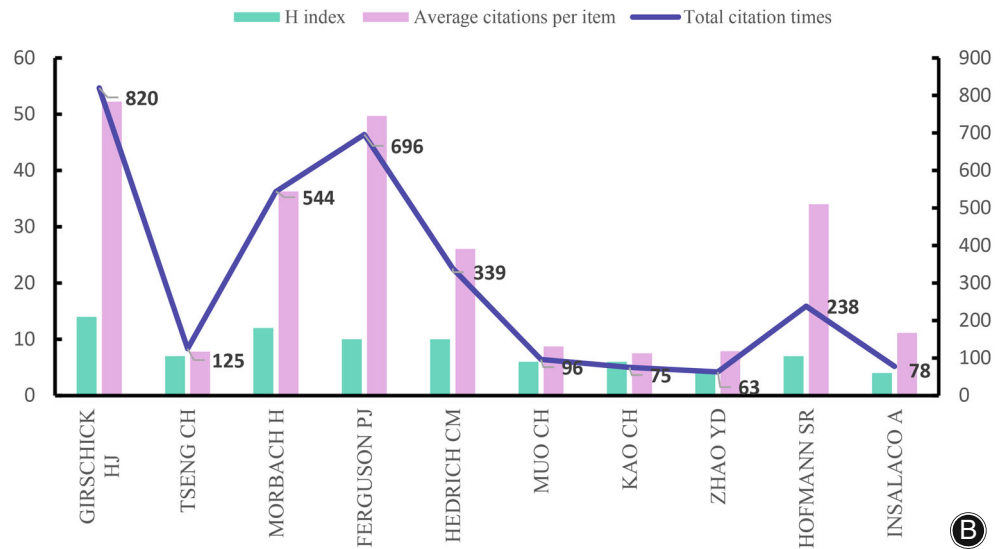
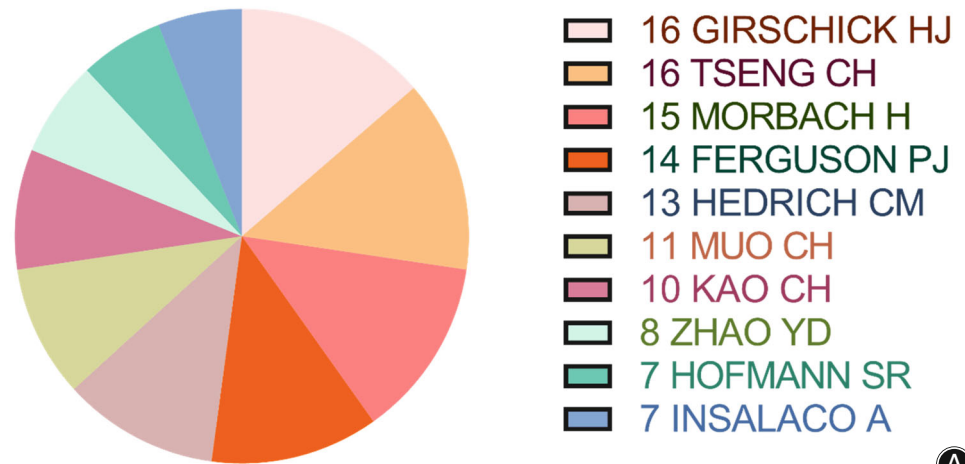
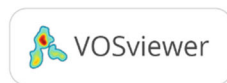


Fig. 4 (A) Top 10 authors of publications number. (B) Author literature quality index. (C) Co-citation analysis of author



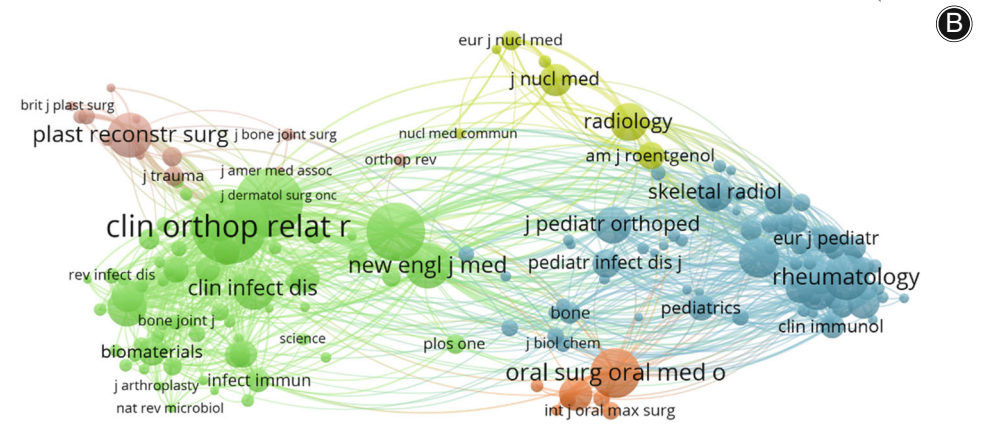
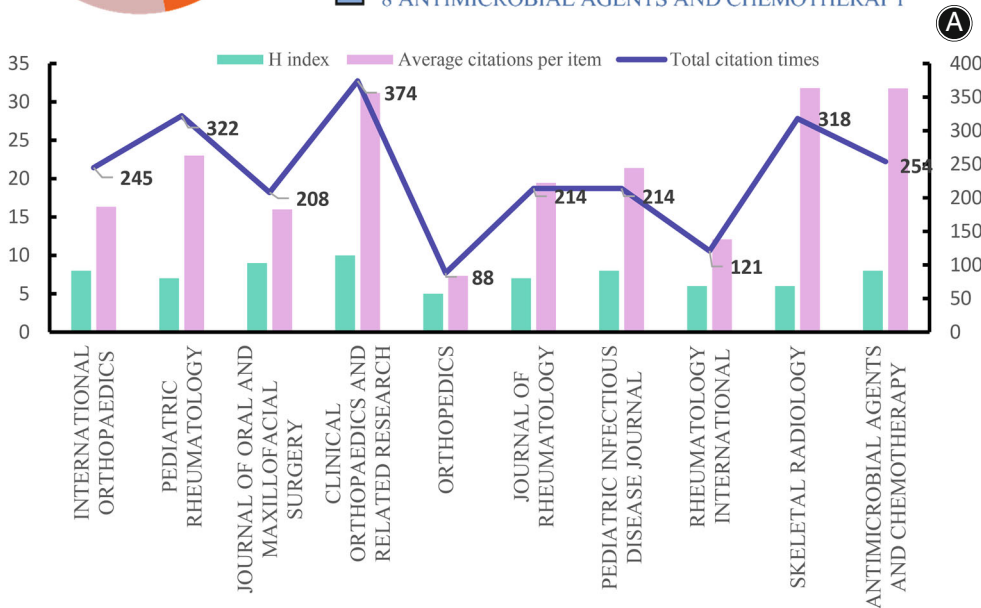
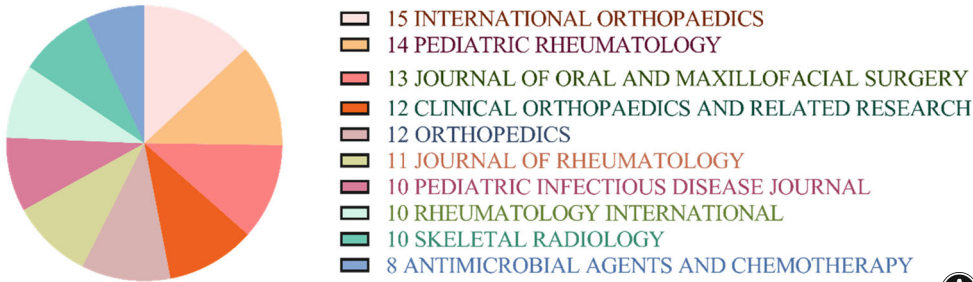
the hotspots of future research are mostly concentrated in module 5.

Discussion

The research related to COM has gained increased interest in the past decade. This study found that the United States and Girschick HJ are the country and

author with the greatest contribution in the field of COM. UNIV IOWA, UNIV WURZBURG and *Clinical Orthopedics and Related Research* are the most influential institutions and journal in this field. Additionally, the efficacy of perforator flap and fascia flap covering soft tissue, searching exclusive detection methods for the diagnosis of COM and bisphosphonates and biological agents in the

The top journals



(A) Top 10 journals of publications number. **(B)** Journal literature quality index. **(C)** Co-citation analysis of source journal

treatment of CRMO may lead to the development of the COM field.

Global Research Status of COM

Generally speaking, the number of articles related to COM shows a trend of wavy growth as a whole. It is expected that the annual publication number of COM will remain at more than 50 in the next decade. This may be related to the great

difficulty in the radical treatment of COM, the enormous consumption of medical resources, and the progressive concern of orthopaedic scholars. In the country literature quality evaluation and co-author analysis of COM, the United States occupies a prominent leading position and cooperates most closely with other countries, which is closely related to the strong economic support and recognized academic status of the United States. In the literature quality assessment and

TABLE 1. Top 10 cited pieces of literature in the field of chronic osteomyelitis (COM)

Rank	Topic	Journal	JCR square	Impact factor	Citations	Publication year	Type	Major conclusion
1	Homozygous mutations in LPIN2 are responsible for the syndrome of chronic recurrent multifocal osteomyelitis and congenital dyserythropoietic anemia (Majeed syndrome)	<i>Journal of Medical Genetics</i>	Q1	4.943	244	2005	Basic research	Homozygous mutations in LPIN2 result in Majeed syndrome. Understanding the aberrant immune response in this condition will shed light on the etiology of other inflammatory disorders of multifactorial etiology including isolated CRMO, Sweet syndrome, and psoriasis.
2	Osteomyelitis and the role of biofilms in chronic infection	<i>Fems Immunology and Medical Microbiology</i>	Q2	3.078	230	2008	Basic research	Taking <i>Staphylococcus aureus</i> as an example, the current understanding of the properties of biofilms and the influence of molecular interactions between bacteria and their hosts on biofilm development and phenotypes are summarized.
3	Systemic antibiotic therapy for chronic osteomyelitis in adults	<i>Clinical Infectious Diseases</i>	Q1	8.313	194	2012	Surgical study	The optimal time of antibiotic use and debridement methods for chronic osteomyelitis were summarized.
4	The accuracy of diagnostic imaging for the assessment of chronic osteomyelitis: A systematic review and meta-analysis	<i>Journal of Bone and Joint Surgery- American Volume</i>	Q1	4.578	174	2005	Diagnosis-related research	FDG PET has the highest diagnostic accuracy in identifying or excluding chronic osteomyelitis. Leukocyte scintigraphy has a proper diagnostic accuracy in peripheral bones, but FDP is more advantageous in the diagnosis of axial bone chronic osteomyelitis.
5	Chronic recurrent multifocal osteomyelitis: Clinical outcomes after more than 5 years of follow-up	<i>Journal of Pediatrics</i>	Q1	3.7	169	2002	CRMO research	Long-term clinical outcomes in children with CRMO appear to be generally good, with most subjects having no evidence of disease activity or sequelae.
6	Fluorine-18-FDG PET and technetium-99m antigranulocyte antibody scintigraphy in chronic osteomyelitis	<i>Journal of Nuclear Medicine</i>	Q1	7.887	165	1998	Diagnosis-related research	In peripheral bone, FDG PET and combined TC-99m-AGAB / (TC)-T-99m-MDP scan are suitable imaging modalities for the diagnosis of chronic osteomyelitis.
7	Chronic osteomyelitis: Detection with FDG PET and correlation with histopathologic findings	<i>Radiology</i>	Q1	7.931	156	1998	Diagnosis-related research	FDG PET can noninvasively detect and display the degree of chronic osteomyelitis with high accuracy. Especially in the central bone where the bone marrow is active, FDG PET has a high accuracy and has great promise in the diagnosis of chronic osteomyelitis.
8	Imaging of chronic recurrent multifocal osteomyelitis	<i>Radiographics</i>	Q1	4.967	154	2009	CRMO research	The imaging features and disease distribution of chronic recurrent multifocal osteomyelitis were summarized.

TABLE 1 Continued

Rank	Topic	Journal	JCR square	Impact factor	Citations	Publication year	Type	Major conclusion
9	Chronic non-bacterial osteomyelitis in children	<i>Annals of the Rheumatic Diseases</i>	Q1	16.102	139	2005	CRMO research	Chronic nonbacterial osteomyelitis in children is an inflammatory spectrum in which CRMO is the most severe. Most children with CNO have a good outcome from the disease. Severe relapses may require oral glucocorticoids FDG-PET may prove to be the preferred study in the management of patients with possible chronic osteomyelitis.
10	Exclusion of chronic osteomyelitis with F-18 fluorodeoxyglucose positron emission tomographic (FDG PET) imaging	<i>Clinical Nuclear Medicine</i>	Q1	6.622	134	2000	Diagnosis-related research	

Abbreviations: CNO, chronic non-bacterial osteomyelitis; COM, chronic osteomyelitis; CRMO, chronic recurrent multifocal osteomyelitis; FDG PET, fluorodeoxyglucose positron emission tomographic.

co-analysis of the authors, Girschick HJ is the scholar with the most contributions in the COM field and the most collaborations with other scholars. It is helpful for us to grasp the authoritative dynamics in this field to pay attention to Girschick HJ's research direction. In the literature quality assessment and co-analysis of institutions, Univ Iowa is a relatively influential institution and in the COM field, but it does not have a dominant position and is almost equivalent to Univ Wurzburg. Scholars may consider these two institutions for further exchange and study. In the evaluation of literature quality and co-citation analysis of journals, the literature of *Clinical Orthopedics and Related Research* have the highest recognition of readers. The high-quality literature of COM is more likely to be published on this journal in the future.

In the top 10 cited articles, "Homozygous mutations in LPIN2 are responsible for the syndrome of chronic recurrent multifocal osteomyelitis and congenital dyserythropoietic anemia (Majeed syndrome)" elaborated on the etiology and mechanism of CEMO caused by genetic LPIN2. "Osteomyelitis and the role of biofilms in chronic infection" discussed the current understanding of the properties of biofilms and the possible effects of molecular interactions between bacteria themselves and between bacteria and hosts on the development and phenotype of biofilms, which systematically showed us the outline of the biofilm field of COM. "Systemic Antibiotic Therapy for Chronic Osteomyelitis in Adults" investigated the optimal time of using antibiotics for the treatment of chronic osteomyelitis and debridement methods, which provided a future research direction for orthopaedic scholars. The diagnosis of COM was the research spot with the largest proportion of references cited in the top 10. Furthermore, all four pieces of literature affirmed the effective value of FDG-PET in the diagnosis of COM and guided clinical application. Two pieces of literature explored the clinical results of CRMO treatment in children, which showed a good prognosis of CRMO in children.

COM Module Co-Occurrence Results Analysis

Detailed analysis of keyword co-occurrence results will help us to grasp the research hotspots of COM in the future. Hence, this study focuses on analyzing the research hotspots predicted in module 3 and 5.

Module 1 relates to COM surgical research. The surgical treatment of COM mainly involves three aspects: local debridement, treatment of bone defect, and elimination of soft tissue cavity. First of all, debriding completely is the key to a successful operation. Rachid *et al.* even proposed that COM lesions should be treated as malignant tumors for over clearing to achieve the effect of complete debridement.^{16,17} Subsequently, the problem that had to be faced was soft tissue and bone defects. There is still controversy about the treatment of bone defects with internal and external fixation. The study of Wang *et al.* showed that there was no significant difference between the two methods for bone defects smaller than 4 cm, but external fixation showed a strong

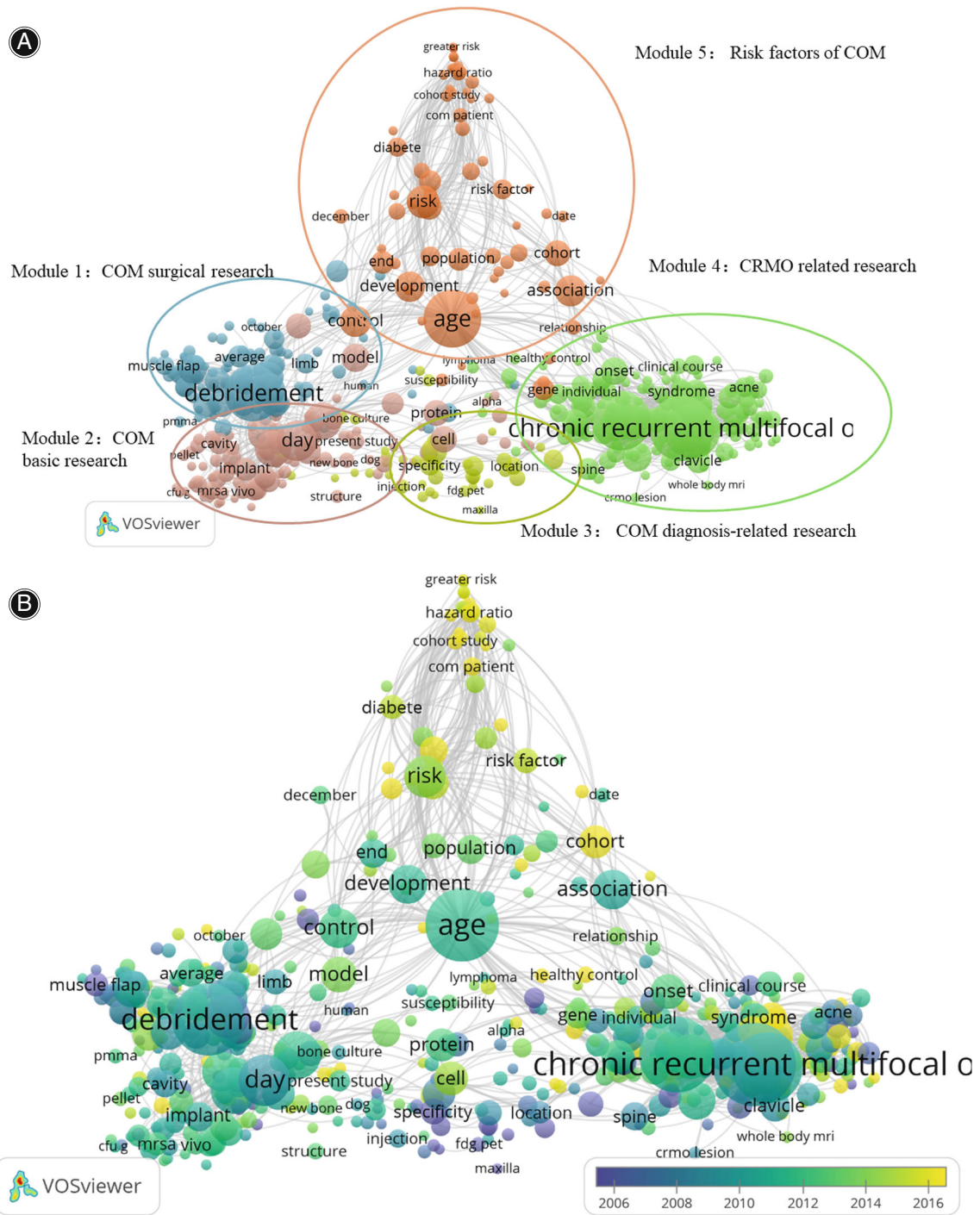


Fig. 6 Keyword co-occurrence analysis diagram. (A) Keywords module analysis diagram. (B) A convergence map of hot words

advantage instability when it was larger than 4 cm.¹⁸ Currently, the more popular fixation technology is Ilizarov, which is not suitable for doctors in most grass-roots hospitals due to its long learning curve, long course of treatment, increased surgical trauma, and risk. Therefore, more studies may focus on simple and effective external fixation techniques in the treatment of bone defects in the future. In the

study of soft tissue defects, vascular latissimus dorsi and rectus abdominis myocutaneous flaps have been widely used, and the curative effect is confirmed; however, the beauty of healing and the functional activities of the donor area become negative problems in its later stage. Scholars put forward that perforator flap and fascia flap can make up for the defect of esthetic effect compared with muscle flap, but the

comparison of curative effect needs to be further confirmed by more studies.¹⁹

Module 2 relates to COM basic research. The research direction of this module is mainly focused on the *in vitro* biofilm of COM. *S. aureus* is the most common pathogen causing COM.²⁰ The difficulty of COM lay in the formation of bacterial biofilm. Bacterial biofilm can resist not only the host mechanism but also the penetration of most antimicrobial agents through the biofilm. Additionally, the bacteria in the membrane will also form low-toxicity characteristics. Studies have manifested that the formation of *S. aureus* biofilm is closely related to CWA and BEM proteins.²¹ Consequently, scholars suggest that the prophylactic use of recombinant vaccine against CWA and BEM protein may effectively block the formation of biofilm.²² As for anti-biofilm research, the current hotspot still focuses on antibiotic therapy through the biofilm, and there are still many gaps in the study of anti-COM biofilm mechanism, so the future research prospect is great.

Module 3 relates to the diagnosis research of COM. In most patients, additional diagnostic images are essential to identify or rule out active infections. Similar to the results of the top 10 cited above, the most significant keywords are diagnostic terms and FDG-PET. As early as in 2005, a meta-analysis by Termaat *et al.* demonstrated that FDG-PET combined technique was the best diagnostic method.²³ Bacterial culture is the most important link in the diagnosis and treatment of osteomyelitis, but the positive rate of culture is not satisfactory.²⁴ In addition, common imaging techniques for the diagnosis of osteomyelitis include plain film, computed tomography, magnetic resonance imaging, and radionuclide labeling scanning. It is generally suitable for patients 2 weeks after infection, which need to be combined with a variety of imaging examinations for diagnosis. In recent years, Raman spectroscopy and IL-13 α 2 receptor as probe MRI imaging system have been proposed one after another.^{25,26} Nevertheless, there is still no way to achieve 100% diagnostic accuracy. In the diagnosis of COM, we still need to find convenient and accurate detection methods or indicators.

Module 4 relates to CRMO research. CRMO is another name for the aggravated condition of chronic non-bacterial osteomyelitis (CNO). As a matter of fact, CRMO belongs to autonomous diseases, which are most common in children, and the average age of onset is 9 years old.²⁷ CRMO is in a dilemma both in diagnosis and treatment. As there is no gold standard diagnosis currently, we can only rely on an exclusion for diagnosis. The diagnosis of CNO is very challenging because it needs to be distinguished from infectious osteomyelitis and malignant tumors. Whole body MRI is advantageous in distinguishing CNO from alternative diagnoses.²⁸ The main goal of CRMO treatment should be to relieve pain and prevent disease progression and permanent damage of diseased bones, which can usually be treated with non-steroidal anti-inflammatory drugs, glucocorticoids, or bisphosphonates.²⁹ Notwithstanding, more and more evidence supports intravenous bisphosphonate therapy, and

some biological agents such as TNF- α inhibitors have been used in clinics gradually. Bisphosphonates or biological agents may be the first choice for CRMO in the future.^{27,29,30}

Module 5 relates to the risk factors of COM. In terms of risk factors, different types of COM have various pathogenic factors and pathogenic bacteria. Most COM are caused by post-traumatic fracture, diabetes, sickle cell disease, malnutrition, etc. There are the most yellow words concentrated on this module, in other words, the hotspots of future research are the most. However, after searching the relevant literature, it is found that the current literature is sparse on the risk factors of COM. Thus, this module is a research direction in which scholars should invest a lot of energy to seek a breakthrough in the field of COM for the future.

Strengths and Limitations

To our knowledge, this is the first study to investigate the status and future hotspot of COM research. Undeniably, there are some limitations in this study. First of all, this study only searched the WOS database, and some other large databases, such as PUBMED, were not included, which may cause some bias. In addition, this study only searched articles in the English language, and articles in other languages were not analyzed, which may also lead to some bias.

Conclusion

In a nutshell, COM-related research will continue to develop further in the next decade. The United States is the country with the greatest contribution in the field of COM. Girschick HJ is the scholar who has contributed the most in the field of COM. UNIV IOWA and UNIV WURZBURG are the most influential institutions in this field. *Clinical Orthopedics and Related Research* is a high-quality journal recognized by scholars in this field. The future research hotspots of COM are more likely to focus on simple and effective external fixation techniques in the treatment of bone defects, the efficacy confirmation of perforator flap and fascia flap covering soft tissue, the study of the anti-biofilm mechanism of COM, searching convenient and accurate detection methods or indicators for the diagnosis of COM, bisphosphonates and biological agents in the treatment of CRMO, and the study of pathogenic factors and pathogenic bacteria of COM.

Author Contributions

Conceptualization: Shuihua Xie and Yirong Zeng. Literature search: Jie Li, Jinlun Chen and Xingyu Wang. Data extraction: Jin Li, Pengcheng Ye, Peng Deng and Yijin Li. Software: Haitao Zhang and Jiahao Li. Formal analysis: Jianchun Zeng, Wenjun Feng and Xinyu Qi. Writing: Jinlun Chen, Xingyu Wang and Haitao Zhang. Manuscript revision: Jinlun Chen, Xingyu Wang, Haitao Zhang and Shuihua Xie. The authors read and approved the final manuscript.

Funding Information

This work was supported by National Natural Science Foundation of China (82104882) and Scientific Research

Project of Guangdong Provincial Bureau of Traditional Chinese Medicine (20201099 and 20221130) in the form of covering the consultation fees of data statistical analysis.

Conflict of Interest

The authors have no conflicts of interest to disclose in relation of this article.

Ethics Statement

Not applicable.

Data Availability Statement

The datasets used and/or analyzed during the current study are not publicly available due to feasibility but are available from the corresponding author on reasonable request.

References

- Lew DP, Waldvogel FA. Osteomyelitis. *Lancet*. 2004;364(9431):369–79.
- Shea KW. Osteomyelitis. *N Engl J Med*. 1997;337(6):428–9.
- Hogan A, Heppert VG, Suda AJ. Osteomyelitis. *Arch Orthop Trauma Surg*. 2013;133(9):1183–96.
- van Vliet KE, de Jong VM, Termaat MF, Schepers T, van Eck-Smit BLF, Goslings JC, et al. FDG-PET/CT for differentiating between aseptic and septic delayed union in the lower extremity. *Arch Orthop Trauma Surg*. 2018;138(2):189–94.
- Hake ME, Oh JK, Kim JW, Ziran B, Smith W, Hak D, et al. Difficulties and challenges to diagnose and treat post-traumatic long bone osteomyelitis. *Eur J Orthop Surg Traumatol*. 2015;25(1):1–3.
- Nasser A, Azimi T, Ostadmohammadi S, Ostadmohammadi S. A comprehensive review of bacterial osteomyelitis with emphasis on *Staphylococcus aureus*. *Microb Pathog*. 2020;148:104431.
- Wassif RK, Elkayal M, Shamma RN, Elkheshen SA. Recent advances in the local antibiotics delivery systems for management of osteomyelitis. *Drug Deliv*. 2021;28(1):2392–414.
- Arshad Z, Lau EJ, Aslam A, Thahir A, Krkovic M. Management of chronic osteomyelitis of the femur and tibia: a scoping review. *EFORT Open Rev*. 2021;6(9):704–15.
- Bury DC, Rogers TS, Dickman MM. Osteomyelitis: diagnosis and treatment. *Am Fam Physician*. 2021;104(4):395–402.
- Hou D, Bi X, Mao Z, Fan Y, Hu X, Li X. Biomaterials research of China from 2013 to 2017 based on bibliometrics and visualization analysis. *PeerJ*. 2019;7:e6859.
- Mao X, Chen C, Wang B, Hou J, Xiang C. A global bibliometric and visualized analysis in the status and trends of subchondral bone research. *Medicine*. 2020;99(22):e20406.
- Zhang Y, Zhang T, Liu X, Zhang L, Hong F, Lu M. Research trends of pregnancy with scarred uterus after cesarean: a bibliometric analysis from 1999 to 2018. *J Matern Fetal Neonatal Med*. 2020;35:3555–64.
- Pei W, Peng R, Gu Y, Zhou X, Ruan J. Research trends of acupuncture therapy on insomnia in two decades (from 1999 to 2018): a bibliometric analysis. *BMC Complement Altern Med*. 2019;19(1):225.
- Qiu Y, Yang W, Wang Q, Yan S, Li B, Zhai X. Osteoporosis in postmenopausal women in this decade: a bibliometric assessment of current research and future hotspots. *Arch Osteoporos*. 2018;13(1):121.
- Zhang H, Fan Y, Wang R, Feng W, Chen J, Deng P, et al. Research trends and hotspots of high tibial osteotomy in two decades (from 2001 to 2020): a bibliometric analysis. *J Orthop Surg Res*. 2020;15(1):512.
- Haidar R, Der Boghossian A, Atiyeh B. Duration of post-surgical antibiotics in chronic osteomyelitis: empiric or evidence-based? *Int J Infect Dis*. 2010;14(9):e752–8.
- Vicenti G, Bizzoca D, Cotugno D, Carrozzo M, Riefoli F, Rifino F, et al. The use of a gentamicin-coated titanium nail, combined with RIA system, in the management of non-unions of open tibial fractures: a single centre prospective study. *Injury*. 2020;51(Suppl 3):S86–s91.
- Wang Y, Jiang H, Deng Z, Jin J, Meng J, Wang J, et al. Comparison of monolateral external fixation and internal fixation for skeletal stabilisation in the management of small tibial bone defects following successful treatment of chronic osteomyelitis. *Biomed Res Int*. 2017;2017:6250635.
- Hong JP. The use of supermicrosurgery in lower extremity reconstruction: the next step in evolution. *Plast Reconstr Surg*. 2009;123(1):230–5.
- Tong SY, Davis JS, Eichenberger E, Holland TL, Fowler VG Jr. *Staphylococcus aureus* infections: epidemiology, pathophysiology, clinical manifestations, and management. *Clin Microbiol Rev*. 2015;28(3):603–61.
- Otto M. Staphylococcal infections: mechanisms of biofilm maturation and detachment as critical determinants of pathogenicity. *Annu Rev Med*. 2013;64:175–88.
- Foster TJ, Geoghegan JA, Ganesh VK, Höök M. Adhesion, invasion and evasion: the many functions of the surface proteins of *Staphylococcus aureus*. *Nat Rev Microbiol*. 2014;12(1):49–62.
- Termaat MF, Rajmakers PG, Scholten HJ, Bakker FC, Patka P, Haarman HJ. The accuracy of diagnostic imaging for the assessment of chronic osteomyelitis: a systematic review and meta-analysis. *J Bone Joint Surg Am*. 2005;87(11):2464–71.
- Sheehy SH, Atkins BA, Bejon P, Byren I, Wyllie D, Athanasou NA, et al. The microbiology of chronic osteomyelitis: prevalence of resistance to common empirical anti-microbial regimens. *J Infect*. 2010;60(5):338–43.
- Xiao L, Li T, Ding M, Yang J, Rodríguez-Corrales J, LaConte SM, et al. Detecting chronic post-traumatic osteomyelitis of mouse tibia via an IL-13Rα2 targeted metallofullerene magnetic resonance imaging probe. *Bioconjug Chem*. 2017;28(2):649–58.
- Khalid M, Bora T, Ghaithi AA, Thukral S, Dutta J. Raman spectroscopy detects changes in bone mineral quality and collagen cross-linkage in *Staphylococcus* infected human bone. *Sci Rep*. 2018;8(1):9417.
- Moreno-Mateo F, Perea SH, Oneil KB. Chronic recurrent multifocal osteomyelitis: diagnosis and treatment. *Curr Opin Pediatr*. 2021;33(1):90–6.
- Zhao DY, McCann L, Hahn G, Hedrich CM. Chronic nonbacterial osteomyelitis (CNO) and chronic recurrent multifocal osteomyelitis (CRMO). *J Transl Autoimmun*. 2021;4:100095.
- Buch K, Thuesen ACB, Brøns C, Schwarz P. Chronic non-bacterial osteomyelitis: a review. *Calcif Tissue Int*. 2019;104(5):544–53.
- Simm PJ, Allen RC, Zacharin MR. Bisphosphonate treatment in chronic recurrent multifocal osteomyelitis. *J Pediatr*. 2008;152(4):571–5.