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# Insights in orthopedic surgery 2021

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# Insights in orthopedic surgery: 2021

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# Table of contents

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# Editorial: Insights in orthopaedic surgery: 2021

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KEYWORDS

future, evidence, advances, information, knowledge

Editorial on the Research Topic
Insights in orthopedic surgery: 2021

When we opened up this topic in just past 2020, orthopaedic surgery was moving at a pace and in ways that we could not have predicted even a few decades ago. Certainly, the way we examine, evaluate and investigate our thoughts, behaviors and results continues to change year to year, even month to months. Some of our most spirated debates now incorporate psychosocial nuances of care, honest solutions around preventing opioid-induced deaths and…artificial intelligence Zhou et al. all topics that constituted background noise at the turn of the 21st century. In this context, we thought it would be informative to open up a topic with an open editorial agenda; we asked our thinkers to provide us with a glimpse of orthopaedics today.

What we found was that some issues that have plagued our patients continue to do so although some of the ways we evaluate and treat them have changed dramatically over the years: back pain and symptoms from lumbar disc herniation Wan et al. shoulder dysfunction from rotator cuff tears Zhou et al. and Jin et al. hip fractures and frailty of our older family members Yu et al. and our never ending dance with our microbial co-habitants Kankilic et al. But besides the new knowledge and skills gained over time, the way we analyze what we have done continues to make progress in ways difficult to predict. In addtion to the standard clinical study methodologies, systematic review and meta-analyses, our compendium now includes modalities such as the aforementioned artificial intelligence and modern ways of conceptualizing our research trends and attention through bibliometric analysis, be it for ankle fractures, patellar instability or rotator cuff disease Zeng et al., Zheng et al. and Jin et al.

As we progress through this decade and beyond, what will we see? AI assembled meta-analyses and registry reports? A dashboard that provides live bibliometric data on-demand? A decision aid phone app that is up-to-the-second current on the literature? Wiil the lines between “research” and data-driven patient care blur? What kind of “knowledge” will we be reporting on in 2050? Bone glue that supports weight-bearing, adaptive surgical implants that guide tissue healing, a cell-programming biologic that requires no surgery at all? I am excited to not only find out but to participate and contribute; and hope that you are too.

## Author contributions

JA: Conceptualization, Writing—original draft, Writing—review & editing.

## Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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# The Global Status of Research in Ankle Fracture: A Bibliometric and Visualized Study

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**Background:** Ankle fractures are common lower extremity fractures that pose a significant economic and social burden. This study analyzed the ankle fracture research literature between 2000 and 2021 to clarify the current status of ankle fracture research and predict future research trends.

**Methods:** Publications related to ankle fractures published between 2000 and 2021 were retrieved from the Web of Science Core Collection. Then Bibliometric analysis and Visualized Study were performed by VOSviewer software.

**Results:** A total of 2656 publications were retrieved. The number of publications related to ankle fractures is increasing every year. The top countries and journals in terms of the total number of publications, number of citations, and H-index ranking were USA and foot and ankle int. Lorich DG had the most publications in this field. University of Amsterdam's research group had the biggest number of publications in this field. Co-occurrence analysis clustered the keywords into seven clusters: survival analysis and prognosis study, internal fixation treatment study, treatment study of combined deltoid ligament rupture, treatment study of combined inferior tibiofibular ligament injury, treatment study of posterior ankle fracture, treatment study of postoperative traumatic arthritis of ankle fracture, and treatment study of ankle injury in children.

**Conclusions:** The importance of ankle fractures is increasing year by year with the aging process, and the number of publications related to ankle fractures will not continue to increase in the future. Survival and prognosis studies, internal fixation studies, combined deltoid ligament rupture studies, and combined inferior tibiofibular ligament injury studies may become the future research hotspots in the field of ankle fractures.

**Keywords: ankle fracture, bibliometric, visualization studies, co-authorship analysis, co-citation analysis**

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## INTRODUCTION

Ankle fractures, accounting for 3.9–10.2% of adult fractures, are the most common type of fracture of the lower extremity (1). The incidence of ankle fractures is increasing with the socioeconomic and aging process of the population (2). The occurrence is often found in physical exercise, strenuous labor, and other activities. Due to the complexity of the ankle joint and the variety

of factors that cause injuries, ankle fractures can take many different forms in clinical practice, and improper management can lead to poorly matched and unstable ankle joints, resulting in complications such as ankle arthritis, deformity healing, and dysfunction (3). In recent decades, many scholars have reported a large number of studies on the diagnosis and treatment of ankle fractures, which are important information for the progress of ankle fracture diagnosis and treatment.

Bibliometric, a subdiscipline of library and information science, enables qualitative and quantitative assessment of research trends based on the bibliometric characteristics of bibliographic databases and the relevant contributions of journals, institutions, and countries (4). To further clarify the current state of research and research trends in ankle fractures and to provide evidence for the development of more rational medical measures for the prevention and treatment of ankle fractures. This study used bibliometric methods to analyze the publications related to ankle fractures since 2000 and generated a visual plot to visualize the current status and hotspots of research in this field, to explore future trends, and to provide directional guidance and new ideas for future research on ankle fractures.

# MATERIALS AND METHODS

## Data Sources and Search Strategy

The data were all publicly available and did not require the approval of the Institutional Review Board. Our research methodology is similar to previous bibliometric studies (5–8). Data were obtained from the Web of Science Core Collection, by searching for publications in English between 2000.01.01 and 2021.12.01 (9). The following search terms were used: ankle fracture*, ankle joint fracture*, fracture* of the ankle, fracture* to the ankle, fracture* of the ankle joint, fracture* to the ankle joint. The search terms for randomized controlled trials (RCTs) were: ankle joint fracture*, fracture* of the ankle, fracture* to the ankle, fracture* of the ankle joint, fracture* to the ankle joint, and randomized controlled trial NOT meta*.

## Data Screening and Collection

### Inclusion Criteria

Articles, conference abstracts, reviews, correspondence, conference articles, editorial material, research notes, errata.

### Exclusion Criteria

Literature not relevant to this study, unpublished literature.

### Extracted Information

Publication year, country, number of publications, total citations, average citations per term, H-index, journal, author, institution, and research fund direction.

## Bibliometric Analysis

Microsoft Office Excel 2016 (Microsoft Corporation, Santa Rosa, CA, USA) was used to rearrange and combine the extracted literature in terms of publication year, country, number of publications, total citations, average citations per term, H-index, journal, author, institution, and research fund direction. The basic characteristics of the data were analyzed to generate statistical charts and perform quantitative and qualitative analysis on the statistical charts. The Hi-index, also known as the h-factor, is a new method of evaluating academic achievement and can be an important indicator of a researcher's research-level or measure the impact of a journal or institution (10, 11). The Trend Line function in Microsoft Office Excel 2016 was used to build the predicted publication growth model equation as well.

## Visualized Study

VOSviewer version 1.6.17 (Leiden University Center for Science and Technology Studies, Leiden, the Netherlands) was used to complete co-citation analysis, co-authorship analysis, co-occurrence analysis, and bibliographic coupling analysis and present the results in a graphical format. The associations between authors, institutions, and countries/regions were visualized using weighted total link strength (TLS) lines.

The TLS represents the degree of association between different items, and a larger value means a higher degree of association. In the visual graph, the thickness of the line is used to represent the size of the TLS value.

Co-citation analysis was proposed by Small (12), which takes the literature as the subject of analysis and uses multivariate statistical analysis methods such as cluster analysis to reduce the inter-citation relationships between the subjects of analysis to a relatively small number of categories and present them graphically as a process. This study uses VOSviewer software to calculate and graphically present the co-citation link strength between different items.

Co-occurrence analysis was first proposed by Callon M (13), by counting and hierarchically clustering the number of occurrences of different items in the same literature, revealing the degree of association between items, and thus clarifying the changes in research directions and hotspots represented by a different item. We use VOSviewer to quantify and graphically display the different classifications and determine future research trends based on this.

Bibliometric coupling firstly proposed by Kessler MM (14) is a more advanced method of literature coupling research. If two articles A and B cite the same literature, there is a coupling between them, indicating that the two articles have similar research content. We use VOSviewer to quantify and graphically display the coupling between the literature.

# RESULTS

## Trends of Global Publication

### Number and Trend of Publications

Since 2020-2021, there was an overall upward trend in the number of ankle fracture-related publications (**Figure 1**), with the highest number of publications published in 2021 ($n$ = 263; 9.9%). The predicted publication growth model equation based on historical data was $y = 0.0225x^3\text{-}0.3975x^2 + 10.563x$, $R^2 = 0.9536$, with x representing the year and y representing the predicted number of publications per year. According to this equation, the number of publications in this field is expected to exceed 600 in 10 years. The total number of articles published

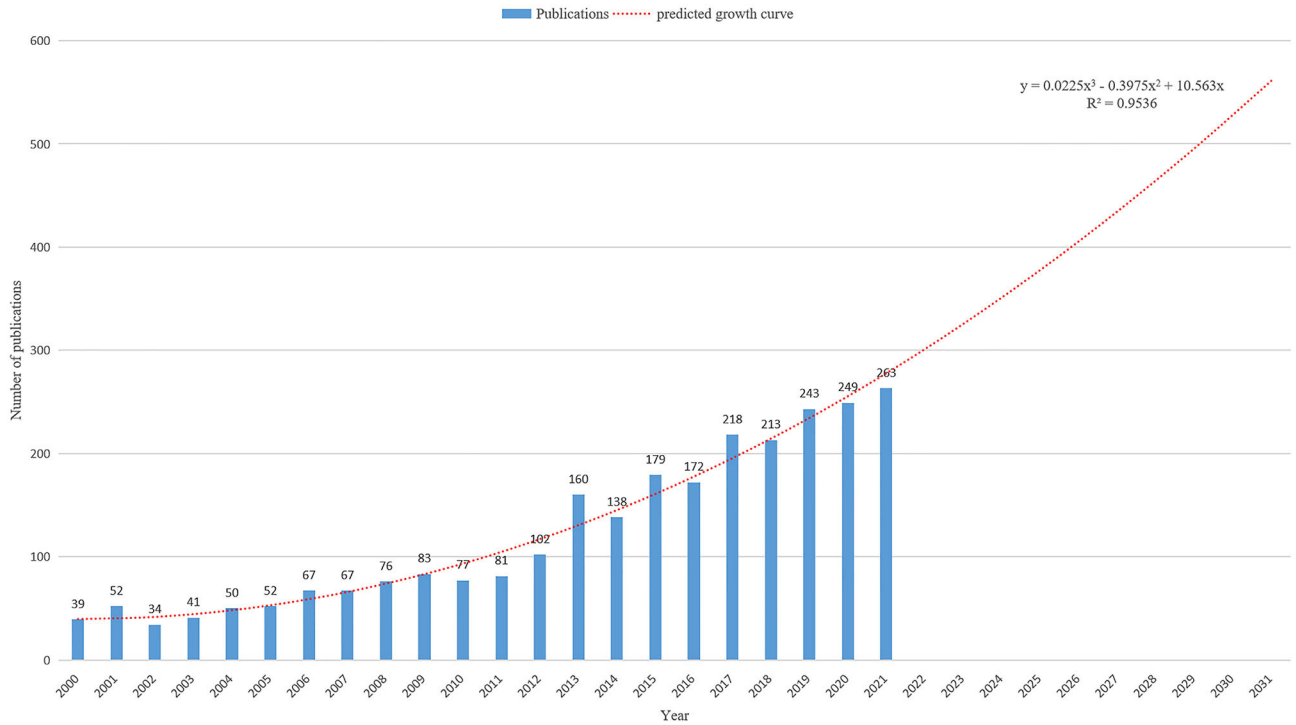


**FIGURE 1 |** The number of publications by year and the predicted growth curve of ankle fractures.

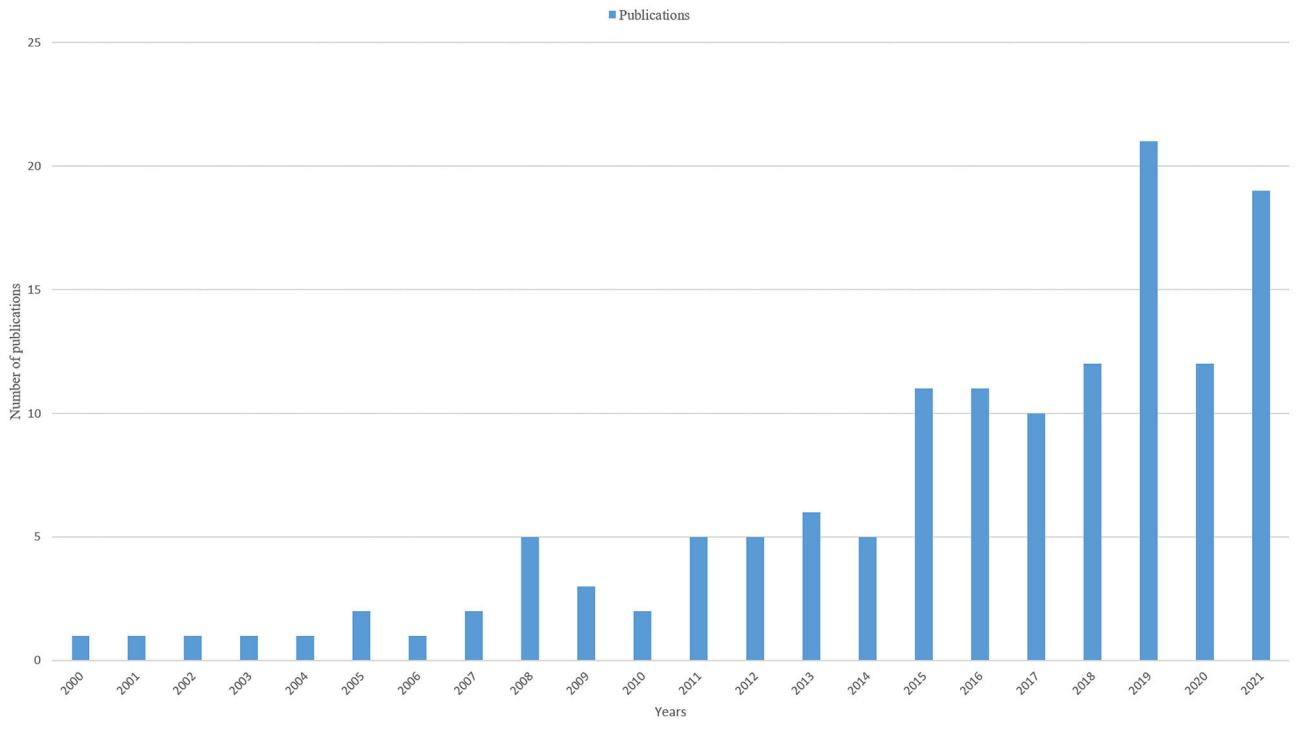


**FIGURE 2 |** The number of publications of RCTs by year.

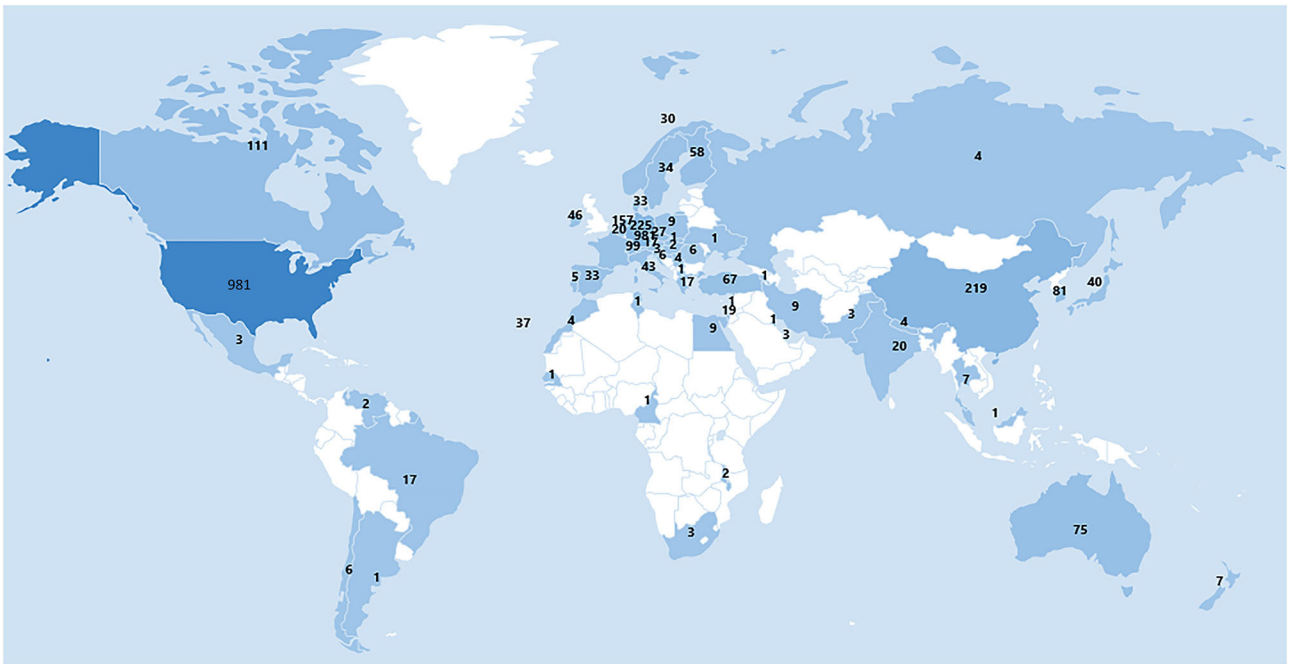


**FIGURE 3 |** Distribution map of publications in different country/region.

in RCTs from 2001 to 2021 is 137, with the most number of publications in 2019 ($n = 21$; 15.3%) (**Figure 2**).

## Contribution of Each Country/Region

A total of 66 Countries/Regions contributed published articles regarding ankle fractures (**Figure 3**). The United States had the highest number of publications in this area ($n = 981$; 36.9%), followed by England ($n = 303$; 11.4%), Germany ($n = 225$; 8.5%), China ($n = 219$; 8.25%) and the Netherlands ($n = 157$; 5.91%).

## Quality of the Publications of Each Country/Region

The United States had the highest H-index (H-index = 75), followed by England (H-index = 36), Germany (H-index = 31), and China (H-index = 21). The United States also had the most total citations ($n = 20,831$), followed by the England ($n = 4,174$), the Netherlands ($n = 4,008$), Germany ($n = 3,223$), and Canada ($n = 2,298$). The publications from the Netherlands had the highest average citation per term ($n = 25.53$), followed by the USA ($n = 21.23$), Australia ($n = 20.6$), and Switzerland ($n = 20.04$) (**Figure 4**).

## Analysis of Global Publication Trends

### Journals

*Foot & Ankle International* had the most publications regarding ankle fractures ($n = 307$, 11.56%), followed by *Journal Of Foot & Ankle Surgery* ($n = 238$, 8.96%), *Injury-international Journal Of The Care Of The Injured* ($n = 209$, 7.87%), and *Journal Of Orthopedic Trauma* ($n = 189$, 7.11%), Journal Of Bone And Joint Surgery -American Volume ($n = 93$, 3.50%). *Foot & Ankle International* also had the highest number of citations ($n = 6,336$), followed by the *Journal Of Orthopedic Trauma* ($n = 5,114$), *Journal of Bone and Joint Surgery-American Volume* ($n = 3,470$), and *Injury-international Journal Of The Care Of The Injured* ($n = 2,823$). *Clinical Orthopedics and Related Research* were $n = 2,537$. *Journal Of Bone And Joint Surgery-American Volume* had the highest impact factor (IF = 5.284), followed by *Clinical Orthopedics and Related Research* (IF = 4.171) (**Figure 5**).

### Research Areas

Of the 62 research areas, the top 10 are Orthopedics, Surgery, General Internal Medicine, Emergency Medicine, Sport Sciences, Endocrinology Metabolism, Radiology Nuclear Medicine Medical Imaging, Rheumatology, Research Experimental Medicine, Pediatrics (**Figure 6**).

### Authors

The ten authors with the biggest number of publications are Lorich DG ($n = 38$), Rammelt S ($n = 36$), Egol KA ($n = 32$), Schepers T ($n = 32$), Kwon JY ($n = 28$), Helfet DL $n = 24$), Ornetta P ($n = 22$), Hoogendoorn JM ($n = 19$), Van Den Bekerom MPJ ($n = 19$), Van Dijk CN ($n = 19$) (**Table 1**).

### Institutions

The top ten institutions with the biggest number of publications are University of Amsterdam, Harvard University, Hospital for Special Surgery, Academic Medical Center Amsterdam, University of Texas System, University of California System, Pennsylvania commonwealth system of higher education, New York University, Technische Universitat Dresden, Massachusetts

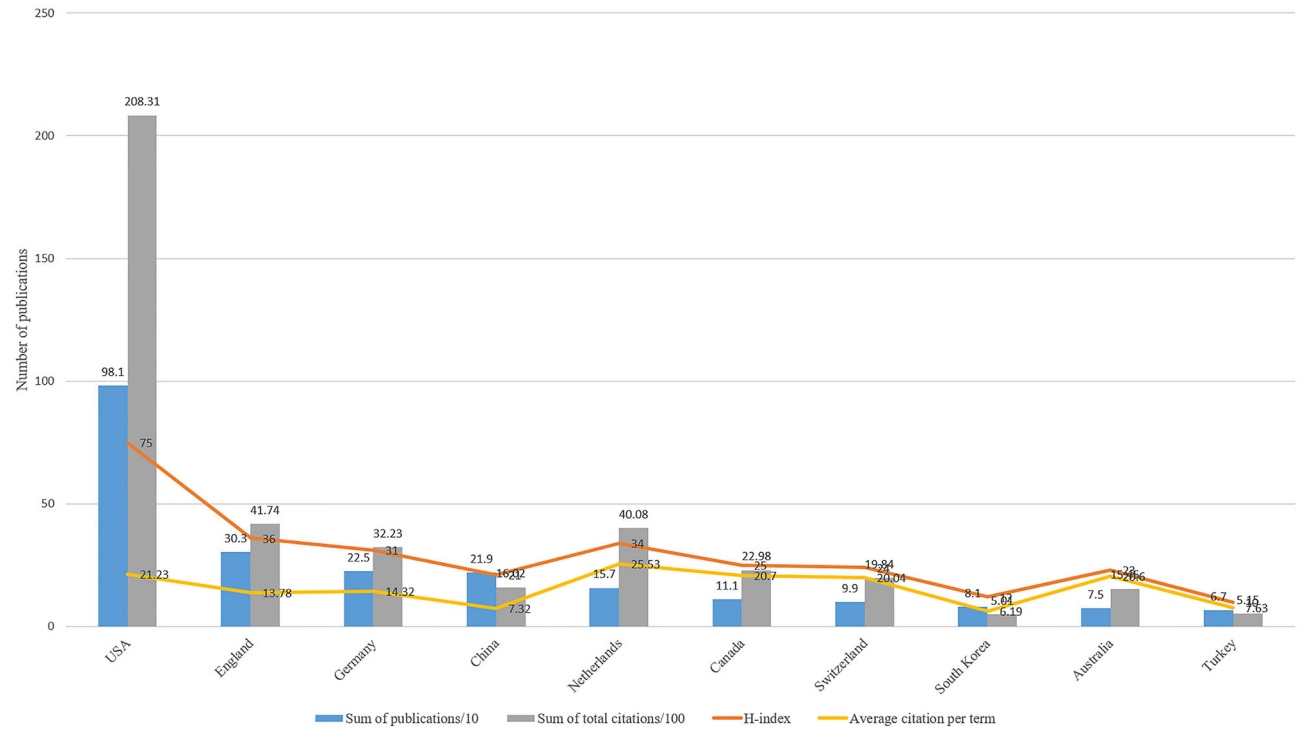


**FIGURE 4 |** The top 10 productive and cited country/region in ankle fracture research.

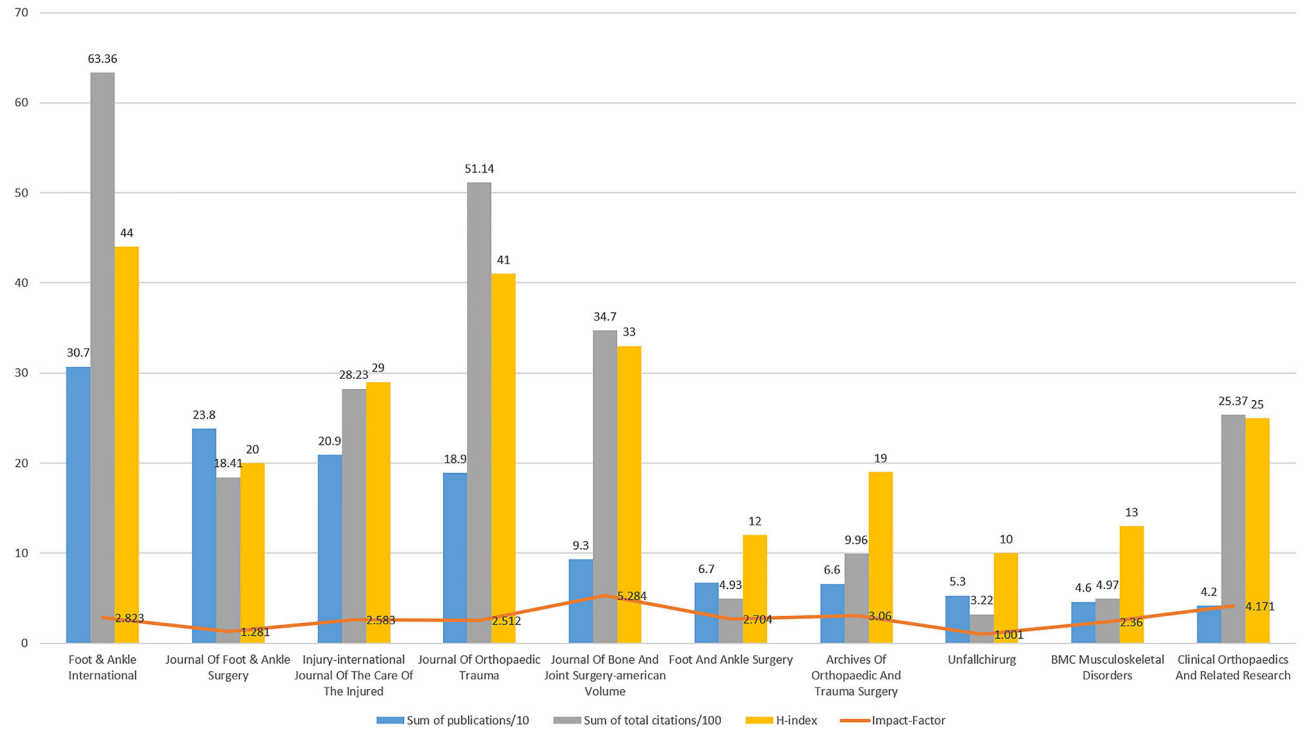


**FIGURE 5 |** The top 10 productive and cited journals in ankle fracture research.

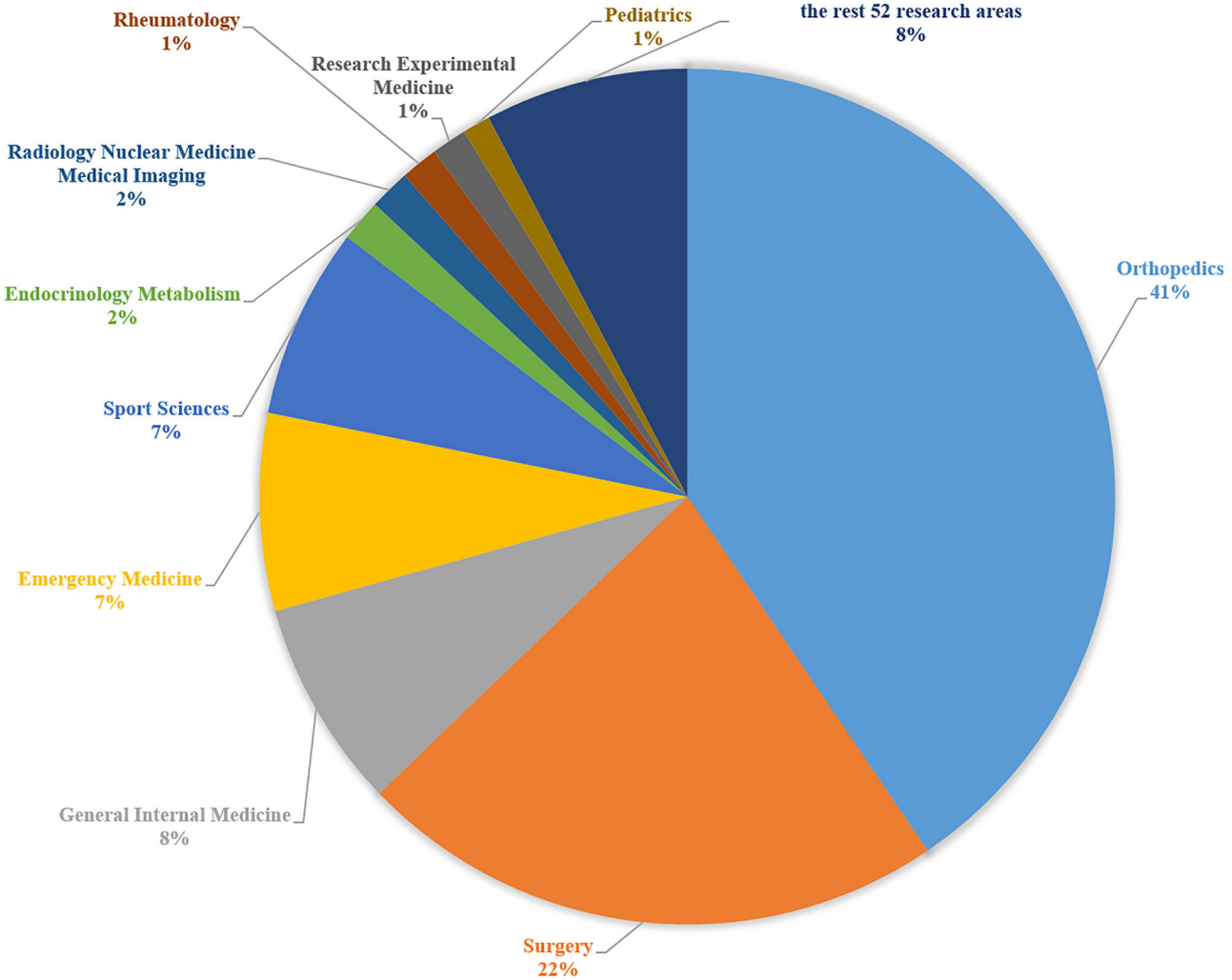


**FIGURE 6 |** The top 10 research directions of ankle fractures.

General Hospital, and the above 10 institutions located in Western countries (7 in the USA, 2 in the Netherlands and 1 in Germany) (**Table 2**).

### Funding Organizations

United States Department of Health Human Services funded the most publications ($n$ = 54; 2.0%), followed by National Institutes of Health ($n$ = 51; 1.92%) and National Natural Science Foundation of China ($n$ = 31; 1.167%). Six of the top ten funding agencies are located in the United States (**Table 3**).

## Co-authorship Analysis

### Authors

A total of 177 authors had at least five publications. Lorich DG had the highest number of TLS (TLS = 101), followed by Helfet DL (TLS = 71), Garner MR (TLS = 55), Schottel PC (TLS = 52), and Pakarinen H (TLS = 51).

### Institutions

A total of 207 institutions had at least five publications. The five institutions with the highest number of TLS were hospital special surgery (TLS = 56), University Toronto (TLS = 46), Massachusetts general hospital (TLS = 39), University Pittsburgh (TLS = 39), McMaster University (TLS = 33).

### Countries/Regions

A total of 39 countries have at least five publications. The five countries with the highest number of TLS markings are the United States (TLS = 176), Germany (TLS = 101), England (TLS = 96), Canada (TLS = 83), and Netherlands (TLS = 69).

## Bibliometric Coupling Analysis

### Authors

A total of 177 authors have at least five publications. The five authors with the highest number of TLS are Lorich DG (TLS =

**TABLE 1 |** The top 10 productive and cited authors in ankle fracture research.

| Authors | Publications | Citations | Average per item | H-index | Country/Region | Institution |
|---|---|---|---|---|---|---|
| Lorich DG | 38 | 1,526 | 40.16 | 17 | USA | Hospital for Special Surgery |
| Rammelt S | 36 | 553 | 15.36 | 13 | Germany | University Hospital Carl Gustav Carus |
| Egol KA | 32 | 1,060 | 33.13 | 18 | USA | NYU-Hospital for Joint Diseases |
| Schepers T | 32 | 735 | 22.97 | 14 | Netherlands | University of Amsterdam |
| Kwon JY | 28 | 180 | 6.43 | 7 | USA | Massachusetts General Hospital |
| Helfet DL | 24 | 1,259 | 52.46 | 16 | USA | Hospital for Special Surgery |
| Tornetta P | 22 | 609 | 27.68 | 15 | USA | Boston University Medical Center |
| Hoogendoorn JM | 19 | 287 | 15.11 | 10 | Netherlands | Haaglanden Medical Center |
| Van Den Bekerom MPJ | 19 | 610 | 32.11 | 14 | Netherlands | Onze Lieve Vrouwe Gasthuis Hospital |
| Van Dijk CN | 19 | 791 | 41.63 | 13 | Netherlands | University of Amsterdam |

**TABLE 2 |** The top 10 productive and cited institutions in ankle fracture research.

| Institutions | Publications | % of total publications | Country/ Region | Citations | Average per item | H-index |
|---|---|---|---|---|---|---|
| University of Amsterdam | 67 | 2.523 | Netherlands | 1,772 | 26.45 | 22 |
| Harvard University | 64 | 2.41 | USA | 1,011 | 15.8 | 17 |
| Hospital for Special Surgery | 56 | 2.108 | USA | 1810 | 32.32 | 20 |
| Academic Medical Center Amsterdam | 54 | 2.033 | Netherlands | 1,690 | 31.3 | 22 |
| University of Texas System | 53 | 1.995 | USA | 884 | 16.68 | 14 |
| University of California System | 46 | 1.732 | USA | 924 | 20.09 | 15 |
| Pennsylvania commonwealth system of higher education | 45 | 1.694 | USA | 1,142 | 25.38 | 15 |
| New York University | 42 | 1.581 | USA | 1,310 | 31.19 | 20 |
| Technische Universitat Dresden | 40 | 1.506 | Germany | 628 | 15.7 | 13 |
| Massachusetts General Hospital | 39 | 1.468 | USA | 655 | 16.79 | 14 |

43,945), Pakarinen H (TLS = 38,649), Flinkkila T (TLS = 30,109), Helfet DL (TLS = 29,442), Rammelt S (TLS = 27,264).

### Journals

A total of 80 journals had at least five publications. The five journals with the highest number of TLS were Foot & Ankle International (TLS = 1,886,638), Journal of Foot & Ankle Surgery (TLS = 125,743), Journal of Orthopedic Trauma (TLS = 120, 213), Injury-international Journal of The Care Of The Injured (TLS = 118,406), Journal of Bone And Joint Surgery-American Volume (TLS = 54,472).

### Institutions

A total of 207 institutions have at least five publications. The five institutions with the highest number of TLS are Hospital for Special Surgery (TLS = 52,803), University of OULU (TLS = 38,450), Academic Medical Center Amsterdam (TLS = 27,491), University of Amsterdam (TLS = 26,765), New York Presbyterian Hospital (TLS = 23,127).

### Countries/Regions

A total of 39 countries have at least five publications. The five countries with the highest number of TLS are the USA (TLS = 421,803), Germany (TLS = 160,733), Netherlands (TLS = 147,100), England (TLS = 143,517), and China (TLS = 119,532).

## Co-citation Analysis

### Journals

There were 322 journals cited at least 20 times. The five journals with the highest number of TLS in order were Foot

**TABLE 3 |** The top 10 productive and cited funding agencies in ankle fracture research.

| Funding agencies | Publications | % of total publications | Country/ Region |
|---|---|---|---|
| United States Department of Health Human Services | 54 | 2.033 | USA |
| National Institutes of Health | 51 | 1.92 | USA |
| National Natural Science Foundation of China | 31 | 1.167 | China |
| National Institute For Health Research | 22 | 0.828 | UK |
| National Institute of Arthritis Musculoskeletal Skin Diseases | 18 | 0.678 | USA |
| Stryker | 18 | 0.678 | USA |
| European Commission | 15 | 0.565 | Europe |
| Amgen | 12 | 0.452 | USA |
| National Health And Medical Research Council of Australia | 12 | 0.452 | Australia |
| Synthes | 12 | 0.452 | USA |

& Ankle International (TLS = 208,110), Journal of Bone And Joint Surgery-American Volume (TLS = 191,519), Journal of Orthopedic Trauma (TLS = 161,653), Injury-international Journal of The Care of The Injured (TLS = 109,816), Clinical Orthopedics And Related Research (TLS = 112,802) (**Figure 7**).

### Publications

A total of 490 articles were cited at least 20 times. The five articles with the highest number of TLS were, in order, Lauge-Hansen N (15) (TLS = 4,787), Weening B (16) (TLS = 4,410), Gardner MJ (17) (TLS = 4,023), Court-Brown CM (18) (TLS = 4,002), Ramsey PL (19) (TLS = 3,869) (**Figure 8**).

## Co-occurrence Analysis

A total of 332 keywords were used at least 10 times. Based on this, the keywords were classified into 7 clusters by cluster analysis.

1. Survival analysis and prognostic studies: epidemiology, risk-factors, complication, outcome, risk, obesity, Osteoporosis, woman, diabetes, deep-vein thrombosis, infection, pain, mortality, body-mass index, bone-mineral density, postmenopausal women.
2. Internal fixation treatment studies: internal-fixation, open reduction, osteosynthesis, plate, locking plate, antiglide plate, fibular nail, lag screw, implants, strength, functional outcomes.
3. Treatment study of combined deltoid ligament rupture: Malleolar fracture, stability, reliability, MRI, ultrasonography, stress radiography, complex, deltoid ligament, bimalleolar fracture, medial fracture, supination-eversion fracture, fibular fractures, weber b, lauge-hanse, lateral mallelus, non-operative treatment,
4. Treatment study of combined inferior tibiofibular ligament joint injury: syndesmosis, tibiofibular syndesmosis, screw fixation, diagnosis, stabilization, stabilization, joint, instability, radiographic measurements, rotational malreduction, radiographic evaluation, suture button Operative treatment, classification,
5. Treatment study of posterior ankle fractures: internal-fixtion, classification, posterior malleolar fracture, pilon, trimalleolar fracture, tibial margin, anatomy, classification
6. Treatment study of postoperative traumatic arthritis after ankle fracture: osteoarthritis, arthroscopy, reconstruction, tibia, fibula, repir, talus, inflammation, gait analysis.
7. Treatment study of ankle injuries in children: children, radiography, distal tibial epiphysis, emergency, validation, distal tibia, rules, ankle injury, accuracy (**Figure 9**).

New emerging keywords from 2013 to 2018: inflammation, fibular nail, fragility fracture, geriatric, imaging, accuracy, x-ray, suture-button, deltoid, outcome, studies, syndesmotic injury, open fracture, osteoarthritis, intromedullary, complex, weight-bearing radiography, impact, surgical site infection, fragment, pathoanatomy, tightrope fixation, suture-button, early weight-bearing, fibular, geriatric, fragility fracture, ORIF, osteoarthritis, quality of life, deltoid, MCS, distal fibular fractures, ankle instability, malreduction, posttraumatic osteoarthritis, pathoanatomy (**Figure 10**). After artificially judging the keyword relevance, we can classify the above terms into 4 categories as follows: (1) survival analysis and prognosis studies; (2) internal fixation treatment studies; (3) treatment study of combined deltoid ligament rupture; (4) combined inferior tibiofibular joint ligament injury.

# DISCUSSION

## Global Trends in Ankle Fracture Research

This study provides a comprehensive overview of trends and developments in ankle fractures from 2000 to 2021. The number of articles related to ankle fractures has increased 6.7-fold since 2000, reflecting the importance that the medical community places on the economic and social burden of ankle fractures. The number of relevant publications is also projected to exceed 600 in 10 years by 2031 based on predictive models, suggesting that the research fervor related to ankle fractures will continue to be maintained and increase with the aging process.

## Status and Quality of Global Publications

H-index and total citations are important indicators of the scholarly impact and quality of publications (12). The United States has the highest number of publications and citations and the highest average citation frequency, indicating that it contributes greatly to the field. Some European countries such as the United Kingdom, Germany, the Netherlands, and Switzerland also play an important role in the field of ankle fracture research due to their high H-index and average citation frequency. In Asia, only China and South Korea are in the top 10. In contrast, most of the countries in Southeast Asia, Central Asia, Eastern Europe, and Africa have hardly contributed to this field of research, probably due to the differences in the socio-economic development of each region. The top 10 affiliations in terms of the number of publications all belong to Western countries (7 in the US and 3 in Western Europe), and also the top 10 organizations funded the most number of studies except NSFC

from China and the rest from Western countries (US 6, EU 1, UK 1, Australia 1). The above results suggest that Western countries, especially the United States, still dominate the current direction of ankle fracture research, which also indicates that top-notch research institutions and adequate financial support are essential to improve the overall academic contribution of a country.

Similarly, there was a clear concentration in the statistics of published journals and published authors. The top 10 journals in terms of total published literature on ankle fractures together account for approximately one-third of all literature in the field, especially Foot & Ankle International, which accounts for more than 10%. Lorich DG, Rammelt S, Egol KA, Schepers T, Kwon JY, Helfet DL, Tornetta P, Hoogendoorn JM, Van Den Bekerom MPJ, Van Dijk CN, Van Dijk CN, and ten other authors published 10% of the total number of articles in the literature, which indicates that the above-mentioned journals and authors deserve our attention. Meaningful and groundbreaking results in the field of ankle fracture research are more likely to be published in these journals, and the studies of the above authors are more likely to reflect recent advances in the field of ankle fracture research.

However, our analysis also revealed that although the literature related to ankle fractures is increasing year by year, the absolute and relative number of high-quality RCT studies among them is still quite low (140/2923, 4.89%), and the same was true in 2020 (22/321; 7.85%). Possible reasons for this are as follows: (1) Due to different levels of economic development, registration systems and follow-up of fracture patients are incomplete in many less developed countries. (2) Although the importance of ankle fractures is increasing with the aging process, it is still not receiving enough attention.

## Research Focus on Ankle Fractures

In the first cluster, the article with the highest total link strength is *Adult Ankle Fractures-An Increasing Problem?* (TLS = 4,002), an epidemiological survey of ankle fractures published in 1998 by Court-Brown (18) in *Acta Orthop Scand*, which included outpatients in addition to inpatients as well as more realistic results than other similar epidemiological studies of ankle fractures of the same period. Simultaneously, it is also the first article to classify a large series of ankle fractures into its constituent A0 subgroups. It is concluded by the study that the population with the highest incidence of ankle fractures with increasing longevity was women between the ages of 75 and 84 years, and the typing results showed that type 44-a accounted for 38% of the total amount, type 44-b for 52%, and type 44-c for 10%.

In the second cluster, the article with the highest total link strength is *Predictors Of Functional Outcome Following Transsyndesmotic Screw Fixation Of Ankle Fractures* (TLS = 4,410), a retrospective observational study published in 2005 by Brad Weening and Mohit Bhandari (16) in *J Orthop Trauma* (Level IV). The prognosis of a total of 51 patients with ankle injuries who received syndesmotic screw fixation at 3 university-affiliated hospitals from 1998 to 2001 was reviewed

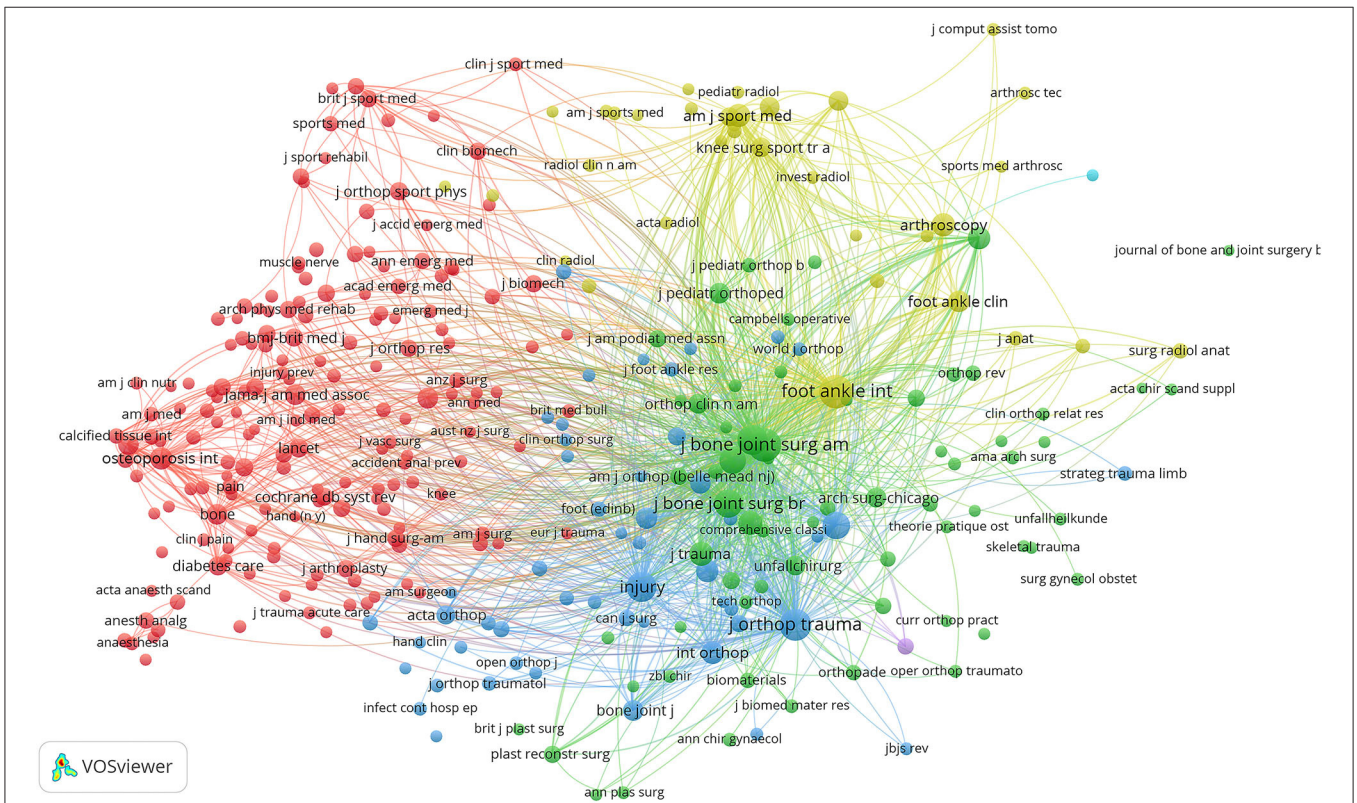


**FIGURE 7 |** Co-citation analysis map of journals on ankle fracture.

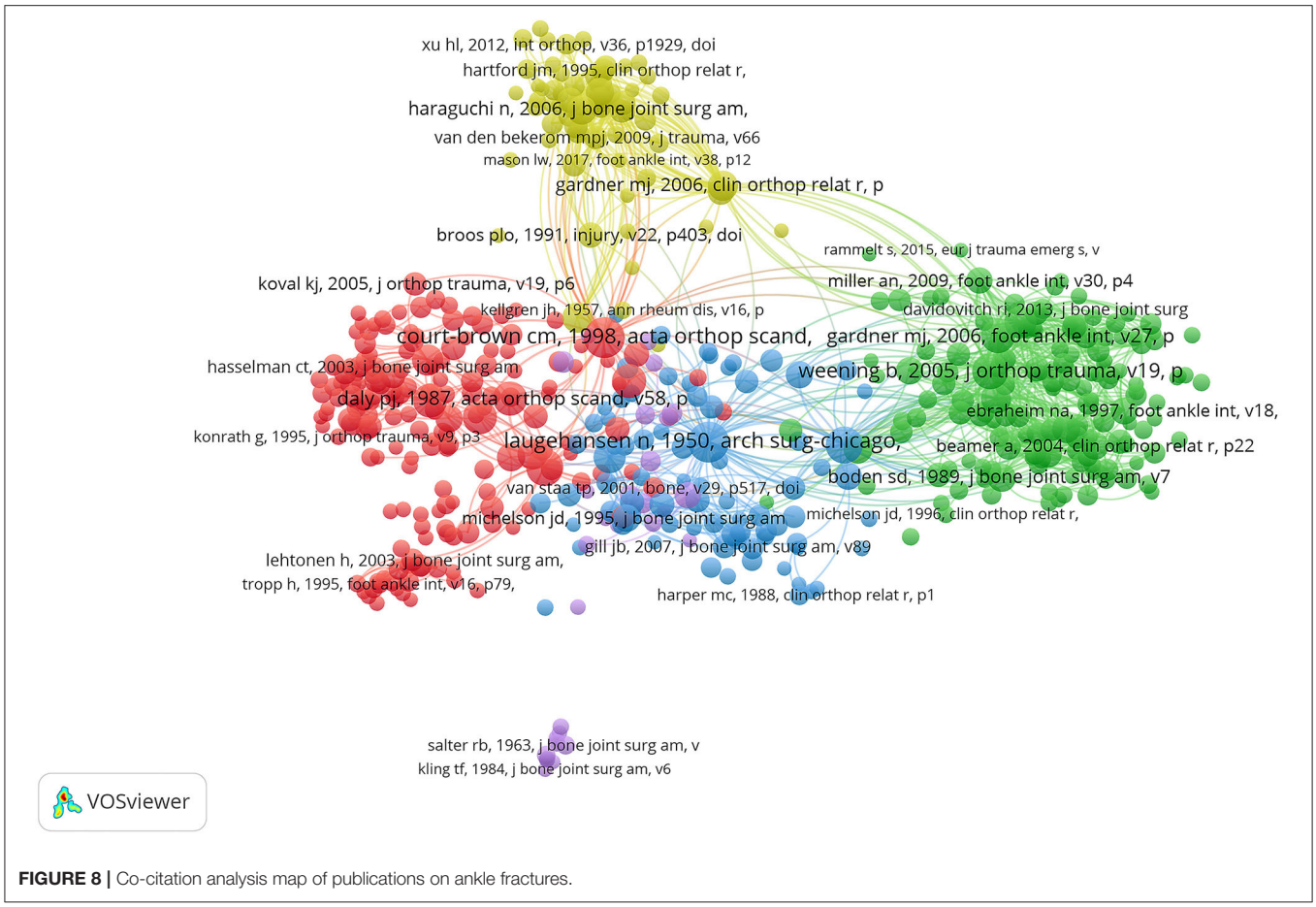


**FIGURE 8 |** Co-citation analysis map of publications on ankle fractures.

in the study and the following results were achieved: (1) 16% of syndesmotic screws may have been unnecessary; (2) The anatomic reduction of syndesmosis was remarkably associated with enhanced Short Musculoskeletal Functional Assessment Index functional outcome.

In the third cluster, the most cited article with the highest total link strength is *Changes In Tibiotalar Area Of Contact Caused By Lateral Talar Shift* (TLS = 3,869), a biomechanical study published in 1976 by Ramsey and Hamiliton (19) in *The Journal of Bone & Joint Surgery*. It is suggested in this article that a lateral displacement of the talus by 1 mm reduces the contact area of the ankle joint by 42%, which in turn leads to uneven pressure distribution in the ankle joint and thereby causes traumatic ankle arthritis. It has been shown by the existing study that the deltoid ligament prevents external rotation of the talus and thus plays a vital role in maintaining the stability of the ankle joint (20, 21). Combined with the study of Ramsey and Hamiliton, it is concluded that ankle fractures with deltoid ligament injury should be treated with aggressive ligament repair therapy.

In the fourth cluster, the article with the highest total link strength is *Anatomy of the Distal Tibiofibular Syndesmosis in Adults: a pictorial essay with a multimodality approach* (TLS = 990), published in 2010 by Hermans (22) in *J Anat*. The description of the anatomy of the separate osseoligamentous structures of the distal tibiofibular joint and discussion of the clinical relevance of these structures were carried out in the above-mentioned anatomical overview, thus it can improve the orthopedic surgeon's understanding and knowledge of anatomy, imaging as well as surgical treatment of distal tibiofibular syndesmosis in adults.

In the fifth cluster, the article with the highest total link strength is *Effect of Posterior Malleolus Fracture on Outcome after Unstable Ankle Fracture* (TLS = 1,634), a prospective study published in 2010 by Tejwani (23) in *J Trauma*, and the prognosis of 309 patients with unstable ankle fractures treated operatively (255 patients without posterior ankle fracture vs. 54 patients with posterior ankle fracture) was followed up. The results showed improvements in function and pain status in all patients at 12 months follow-up, but patients with posterior malleolus fractures had significantly worse total scores and pain function according to the American Orthopedic Foot and Ankle Society score. Similar conclusions were reached on the Short Form-36 questionnaire and the Short Musculoskeletal Function Assessment questionnaire, which were statistically different when the posterior malleolar fracture group scored lower than the unaccompanied posterior malleolar fracture group. It is hereby concluded that patients with posterior malleolus fractures have a worse prognosis.

In the sixth cluster, the article with the highest total link strength is *Posttraumatic Ankle Osteoarthritis after Ankle-Related*

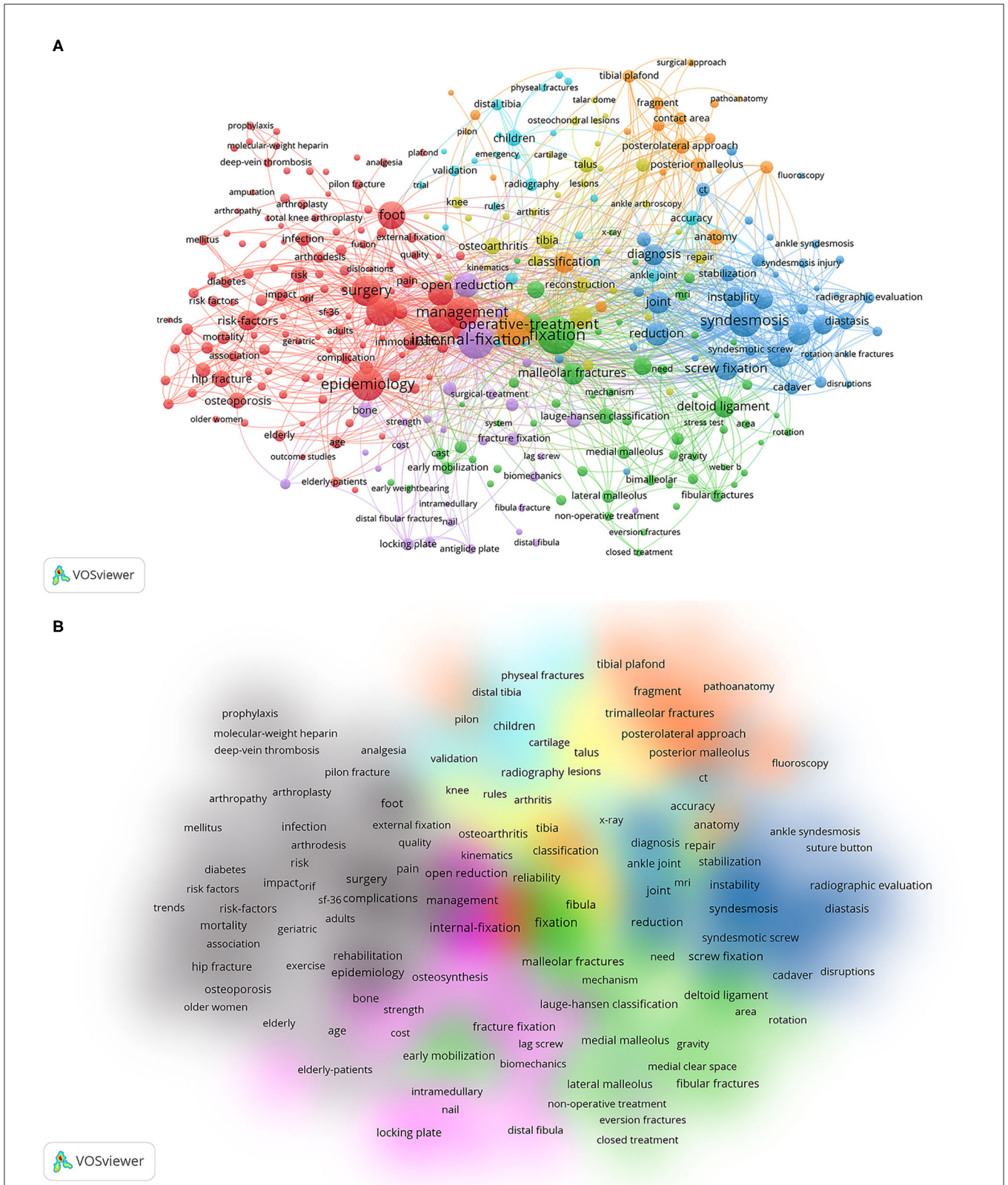


**FIGURE 9 |** Co-occurrence analysis of global research on ankle fractures. **(A)** Keywords-mapping of co-occurrence analysis of global research on ankle fractures. **(B)** Density distribution of co-occurrence analysis of global research on ankle fractures.

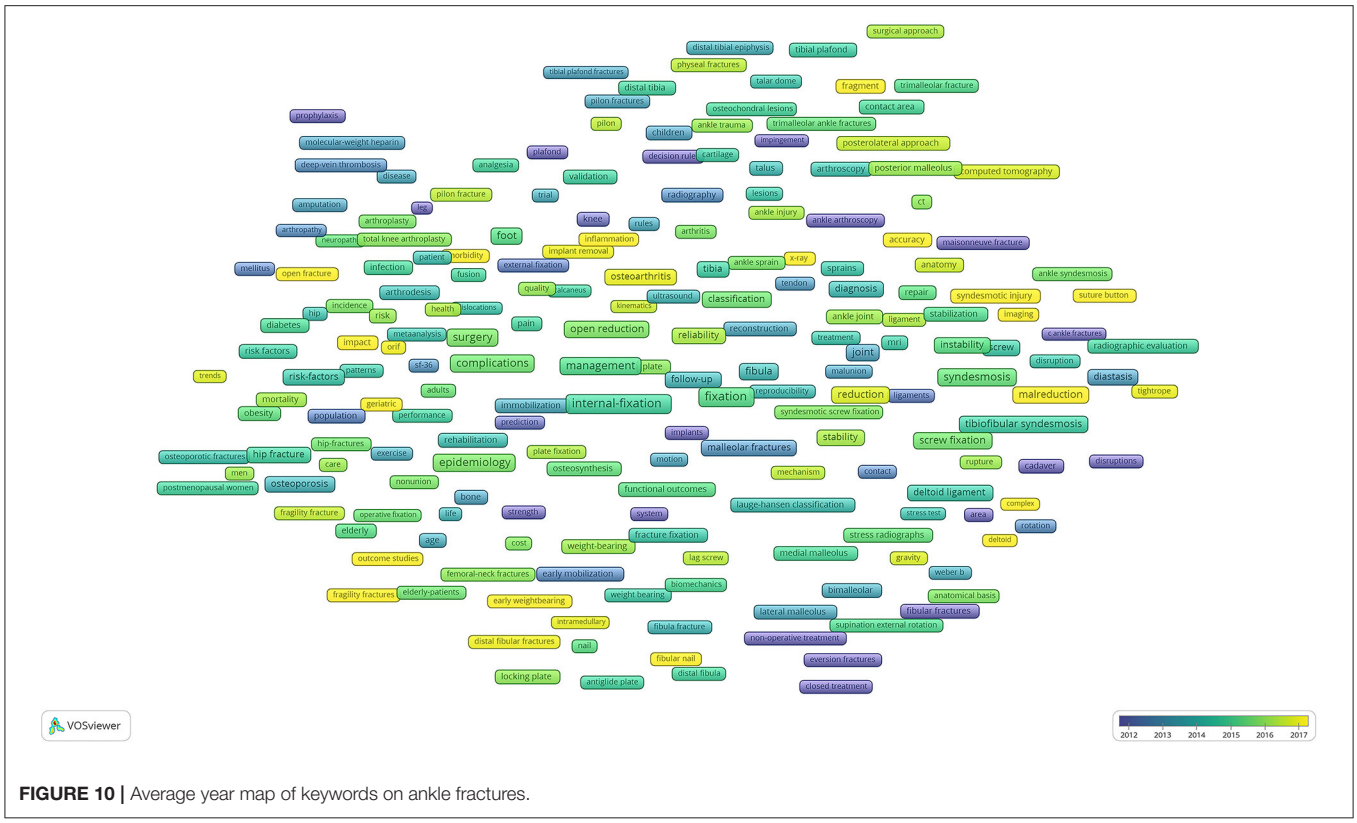


**FIGURE 10 |** Average year map of keywords on ankle fractures.

*Fractures* (TLS = 945), published in 2009 by Monika Horisberger (24) in *J Orthop Trauma*, a retrospective cohort study on 141 patients with a history of ankle-related fractures. This is the first study to analyze the etiology, mechanisms, and risk factors of posttraumatic ankle osteoarthritis (OA). The results showed that ankle fractures were the most common OA-related fractures, accounting for 53.2%. The mean time from OA-related injury to end-stage ankle OA was 20.9 years (1–52 years). The mean time between injury onset and progression to end-stage ankle OA is 20.9 years (1–52 years). OA latency is remarkably shorter in patients with complications during fracture healing and there is a negative correlation between age (at the time of ankle injury) and OA latency.

In the seventh cluster, the article with the highest total link strength is *A Randomized, Controlled Trial of a Removable Brace vs. Casting in Children with Low-Risk Ankle Fractures* (TLS = 288), a randomized, single-blind trial published by Kathy Boutis (25) in *Pediatrics*. The above-mentioned study compared the outcomes of 104 children aged 5–18 years with isolated distal fibular ankle fractures treated with a removable ankle brace ($n$ = 54) or casting ($n$ = 50) and it was shown by the results that plaster fixation remains the standard treatment, but the mean activity score at 4 weeks in the brace group was significantly higher than the score in the cast group (91.3 vs. 85.3%). And the cost-effectiveness acceptability curve was invariably shown to be >80%. Concerning the recovery of physical function, the removable ankle brace is excel in its effectiveness when compared with the cast and is cost-effective as well.

The overlay visualization map showed that the hot spots in ankle fracture research in recent years were survival and prognosis studies, treatment of combined tibiofibular joint ligament injury, internal fixation treatment, and treatment of combined deltoid ligament rupture, which emerged later than the research directions, indicating that there is great potential for follow-up research and researchers can continue to explore these directions in the future.

## LIMITATIONS

The limitations of this study are: (1) The literature included is from one database, which may lead to the inclusion of a small number of articles for analysis compared to the number of real relevant articles; (2) Only English published literature is included, which may lead to language bias and ignore the contribution of non-English literature to the development of the discipline as a whole; (3) Some of the best articles published in recent years, due to their low citation frequency, may also lead to errors in the results.

## CONCLUSIONS

This study illustrates the current state of global research on ankle fractures between 2000 and 2021 and predicts future research trends in this field. Foot & Ankle International can be considered a landmark journal since it has published the highest number of citations on ankle fractures. The survival and prognosis analysis,

the treatment of combined tibiofibular ligament injuries, the treatment of internal fixation, and the treatment of combined deltoid ligament ruptures will be a hot topic of research in the future. We also need to collaborate to conduct more high-quality RCT studies. In addition, we call for the establishment of standardized ankle fracture registry follow-up in Southeast Asian, Eastern European, and African countries as soon as possible, which will help to further improve the global system of ankle fracture management.

## DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## AUTHOR CONTRIBUTIONS

JZ: conceptualization, methodology, software, validation, formal analysis, data curation, writing–original draft, and visualization. JL: conceptualization, methodology, software, validation, and writing–review and editing. GX, WZ, DW, HL, XG, and YX: data curation. CX: visualization and supervision. LZ: project administration and writing–review and editing. PT: project administration, writing–review and editing, and funding acquisition. All authors contributed to the article and approved the submitted version.

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REVIEW
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# Emerging Issues Questioning the Current Treatment Strategies for Lumbar Disc Herniation

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Lumbar disc herniation is among the common phenotypes of degenerative lumbar spine diseases, significantly affecting patients' quality of life. The practice pattern is diverse. Choosing conservative measures or surgical treatments is still controversial in some areas. For those who have failed conservative treatment, surgery with or without instrumentation is recommended, causing significant expenditures and frustrating complications, that should not be ignored. In the article, we performed a literature review and summarized the evidence by subheadings to unravel the cons of surgical intervention for lumbar disc herniation. There are tetrad critical issues about surgical treatment of lumbar disc herniation, i.e., favorable natural history, insufficient evidence in a recommendation of fusion surgery for patients, metallosis, and implant removal. Firstly, accumulating evidence reveals immune privilege and auto-immunity hallmarks of human lumbar discs within the closed niche. Progenitor cells within human discs further expand the capacity with the endogenous repair. Clinical watchful follow-up studies with repeated diagnostic imaging reveal spontaneous resolution for lumbar disc herniation, even calcified tissues. Secondly, emerging evidence indicates long-term complications of lumbar fusion, such as adjacent segment disease, pseudarthrosis, implant failure, and sagittal spinal imbalance, which get increasing attention. Thirdly, systemic and local reactions (metallosis) for metal instrumentation have been noted with long-term health concerns and toxicity. Fourthly, the indications and timing for spinal implant removal have not reached a consensus. Other challenging issues include postoperative lumbar stiffness. The review provided evidence from a negative perspective for surgeons and patients who attempt to choose surgical treatment. Collectively, the emerging underlying evidence questions the benefits of traditional surgery for patients with lumbar disc herniation. Therefore, the long-term effects of surgery should be closely observed. Surgical decisions should be made prudently for each patient.

**Keywords: adjacent segment disease, instrumentation, lumbar disc herniation, lumbar fusion, metallosis**

## INTRODUCTION

As one of the most burdensome health issues globally, low back pain (LBP) causes vast expenditures in treatment and sick leave from work (1). According to the Global Burden of Disease Study 2013, LBP is one of the most common musculoskeletal diseases amongst 301 acute and chronic diseases and injuries based on data from 188 countries during 1990–2013 (2). Degenerative diseases of the intervertebral discs, such as lumbar disc herniation (LDH, MeSH: intervertebral disc displacement), represent part of the most common causes of LBP (3). The prevalence of LDH is 2% in the general population (4) and 1.42% in adolescents (5), according to SweSpine. Except for the presence of cauda equina syndrome, plegia, and sensory-motoric deficits, controversy still exists regarding the indications for surgical intervention.

Whether to choose conservative measures or surgical treatments is still controversial for LDH in some areas (6). The traditional surgical procedures of LDH are various according to the disease, including pure decompression, decompression with non-instrumented fusion, decompression with instrumented fusion, minimally invasive decompression with fusion, decompression associated with a dynamic stabilization system, etc. Patients with isolated herniated lumbar discs causing radiculopathy are recommended to undergo the primary disc excision operation, such as open discectomy, endoscopic discectomy, or laminectomy in the guideline. Lumbar spinal fusion is not recommended as a routine treatment for these patients. However, lumbar spinal fusion is recommended for patients with herniated discs who have severe degenerative changes or obvious intersegmental instability caused by the herniated discs. Besides, reoperative discectomy and fusion is a potential treatment option in patients with recurrent disc herniations associated with significant deformity, instability, or chronic axial low back pain (7). Reoperative discectomy and fusion are believed superior in minimizing mechanical instability and recurrence compared to reoperative discectomy for the recurrent cases (8).

A retrospective study consisting of 18,590 patients with LDH who underwent surgical treatment showed that open discectomy was the most common procedure (68.9%) in the primary operation, followed by endoscopic discectomy (16.1%), laminectomy (7.9%), fusion (3.9%), and nucleolysis (3.2%) (9). Although pure decompression is the most recommended surgical procedure for the purely herniated with neurological symptoms, the reoperation rates were considerably high, with 18.6, 13.8, and 12.4% after laminectomy, open discectomy, and endoscopic discectomy, respectively (9). As a matter of fact, removing part of the lumbar disc might induce a secondary complex situation that can bring spinal instability (10). And it turns out an initial lumbar discectomy for the patients with LDH is statistically associated with an increased likelihood of lumbar fusion in the future (11).

The selection of treatment strategy for LDH should be based on the severity of the disease and the patient's overall condition (12). Whether to choose non-surgical or surgical treatment and which surgical procedure is selected depends on the severity of symptoms and the clinical-pathological correlate. However, the decision-making of treatment strategy is partially preference-sensitive, depending on the surgeon's preference, which is influenced by the doctors' experience and patients' expectations.

Although surgical treatment has been demonstrated as an effective treatment strategy with the advantages, such as rapid symptoms relief, increased stability, facilitated bone healing, and restored alignment, several disadvantages or complications in the long term have also been noted (13). These complications, i.e., adjacent segment degeneration, metallosis, and additional ionizing radiation exposure, have been widely reported in the last two decades. There is accumulating evidence that questions the benefits of traditional surgery for patients with LDH (14, 15). Given that the pros of surgical treatment have been well-documented in the literature, we will emphasize the cons from four aspects in the current review.

## NATURAL HISTORY ISSUE OF LDH

### Immune Privilege of NP

#### Closed Niche

Physiologically, the human lumbar disc comprises three subparts, i.e., the sandwiched central nucleus pulposus (NP), peripheral annulus fibrosus (AF), and adjacent cartilage endplates. The local environment of NP cells is similar to a closed niche (16) (**Figure 1**). Furthermore, the disc belongs to one of the largest avascular structures in the human body. The blood vessels and innervations terminate in the outer layer of AF of the healthy disc (17). The closest distance from the center of NP to the blood supply is as far as 7–8 mm (18). The nutrition of NP mainly derives from the osmosis of cartilage endplate and AF (18, 19). Therefore, human NP in the disc remains untouched from the immune system, being the physiologic basis of human discs as immune-privileged organs.

#### FasL-Fas Network as Underlying Mechanisms of NP Immune-Privilege

FasL (Fas ligand, CD178) localizes in human NP cells strategically as a death factor, which can bind with Fas (CD95, death receptor) of invasive immune cells and endothelial cells (20, 21). The binding of FasL to Fas induces apoptosis (22) of the invasive immune cells, maintaining the immune-privilege characteristic of the intact human NP (23). It has been reported that the cells' morphological alterations and chromosomal DNA degradation in apoptosis occur within a few hours *in vitro* (24).

#### Breakdown of the Immune Privilege and Disc Degeneration

Kaneyama et al. (25) found a significant decrease of FasL expression in the degenerated discs compared with the non-degenerate discs, implying the potential protective role of FasL

**Abbreviations:** NP, nucleus pulposus; AF, annulus fibrosus; ASD, adjacent segment disease; CEP, cartilage endplate; FADD, Fas-associated death domain containing protein; FasL, Fas ligand; IDD, intervertebral disc degeneration; LBP, low back pain; LDH, lumbar disc herniation; lncRNA, long noncoding RNA; miRNA, microRNA; MMP, metalloproteinase; MRI, magnetic resonance imaging; NASS, North American Spine Society; ncRNA, noncoding RNA; RCTs, randomized controlled trials.

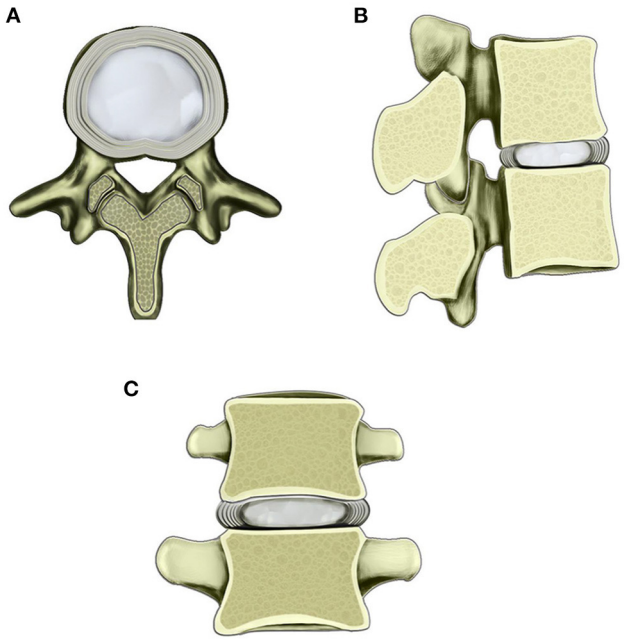


**FIGURE 1 |** Schematic diagram of the normal lumbar disc within the scope of the vertebral body. **(A)** Transverse view of normal lumbar disc. **(B)** Sagittal view of lumbar disc and adjacent vertebral bodies. **(C)** Coronary view of lumbar disc and adjacent vertebral bodies. The border of the central nucleus pulposus and surrounding AF is clear.

against degeneration. Fas and FasL's expression on stabbed-disc cells is significantly higher than those in normal disc cells (26). When the physiological barrier is damaged, an autoimmune reaction is evoked. Immune cells expressing with FasL bind with NP cells expressing with Fas, which induces the NP cells apoptosis. At the same time, up-regulated FasL in NP co-expressing with Fas induces apoptosis of disc cells *via* the paracrine pathway. Deregulated FasL and Fas contributing to the abnormal apoptosis of NP cells may be possible pathogenesis of intervertebral disc degeneration (IDD).

Emerging evidence indicates that various physiologic and pathologic processes are regulated by the coding (mRNAs)-non-coding RNA (ncRNA) network. Types of ncRNAs, such as microRNA (miRNA) and long non-coding RNA (lncRNA), are involved in various physiologic and pathologic processes in IDD, which were reported previously. We found that several miRNAs are differentially expressed in degenerative NP, including the down-regulated miR-155. Further investigation revealed that miR-155 plays a regulatory role in FasL-Fas apoptotic signaling pathway. Deregulated miR-155 increases the expression level of Fas-associated death domain-containing protein (FADD) and caspase-3, promoting Fas-mediated apoptosis in IDD (27). Following that, **a** lncRNA-mRNA microarray analysis of human NP was conducted in 2014 (28). Up-regulated expression of enhancer-like lncRNA RP11-296A18.3 was observed, inducing the overexpression of Fas-associated protein factor-1 which induces the Fas-mediated apoptosis of NP cells at last. Subsequently, Cui et al. indicated that another lncRNA, MAGI2-AS3, is down-regulated in IDD, which is inversely related to the FasL level in NP cells (29). Decrease expression of lncRNA MAGI2-AS3 may promote FasL expression and trigger the FasL-Fas apoptotic signaling pathway, resulting in the apoptosis of NP cells. We addressed the Fas-FasL interacting network between NP, immune cells, and certain modulation factors (21), organizing global researchers for a hot topic issue on IDD (30).

### Endogenous Repair Basis

During the regeneration process of various organs, endogenous repair exists, including liver, gut, skin, muscle, kidney, and bone (31). Each organ has a specific capacity for endogenous repair. Accumulating evidence indicates that endogenous repair exists in the human disc, with progenitor cells as crucial contributors (32, 33). In 2007, Risbud et al. (34) first identified human NP and AF cells expressing specific stem cell types of surface markers from degenerative discs. Moreover, these cells can differentiate into chondrogenic, osteogenic, and adipogenic lineages. After that, multiple lines from *in vivo* and *in vitro* studies indicated the existence of progenitor cells in human intervertebral discs. Intervertebral disc cells expressing Tie 2 represent a subtype progenitor cell group with discogenic differentiation potential and enhanced regeneration (35).

Besides these basic lines of evidence, various clinical factors contribute to the disruption of the barrier, including trauma/microtrauma during daily life, aging/pathologic alterations (such as scoliosis) with cartilage endplate (CEP) degeneration, iatrogenic, congenital factors, and/or vertebral endplate morphology (36).

## Emerging Etiology Evidence of LDH

### Clinical Evidence of Spontaneous Resorption of Herniated Intervertebral Discs

Cribb et al. reported a dramatic regression of massive herniation in 14/15 patients after an average 24 months follow-up (range: 5–56 months) (37). Compared with bulges and focal protrusions, broad-based herniation and sequestrations improve more (38). Not only massive soft herniation but large calcified disc herniation could be absorbed as well (39). Other spinal herniation, such as cervical/thoracic disc herniation with/without calcification, has also been reported with spontaneous resolution (40, 41).

Repeated MRIs revealed the shrinkage of herniated discs gradually, with 76% or more absorbed in 1 year (**Figure 2**). Moreover, Panagopoulos et al. summarized 12 studies in a systematic review (42). Amongst 901 middle-aged LDH patients, 15% to 93% were partially or entirely relieved by 1 year with repeated MRI observations. Zhong et al. conducted a meta-analysis with 11 cohort studies and revealed that the overall incidence of spontaneous regression in LDH patients was 66.66%, with a regional difference (43).

Clinical symptoms, such as sciatica and motor and sensory deficits, can gradually improve in non-surgical treatment LDH cases (44, 45). However, changes in the size of herniated intervertebral discs on MRI are not significantly correlated with the development of clinical symptoms. For instance, sciatica

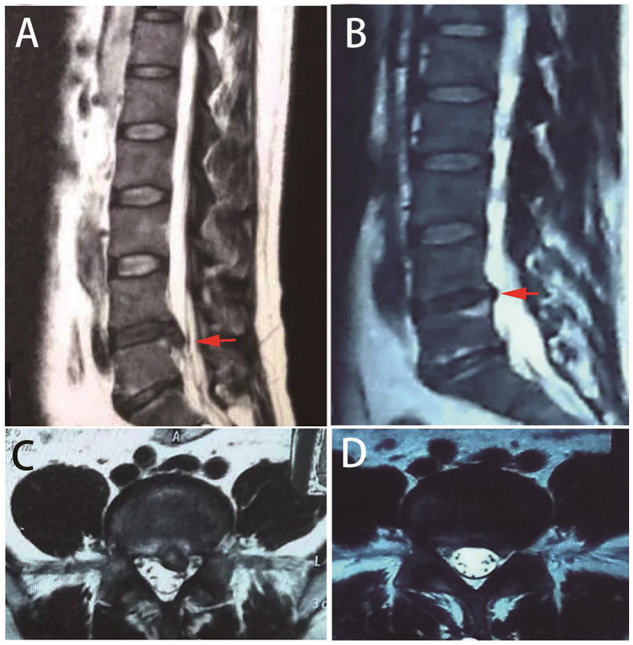


**FIGURE 2 |** Repeated MRIs of a typical case with spontaneous resolution. A 39-year-old male patient presented with low back pain and sciatica. MRI indicates lumbar disc herniation at L5/S1 [**(A,C)** red arrows]. One year later, repeated MRI indicates herniation resolution [**(B,D)** red arrows].

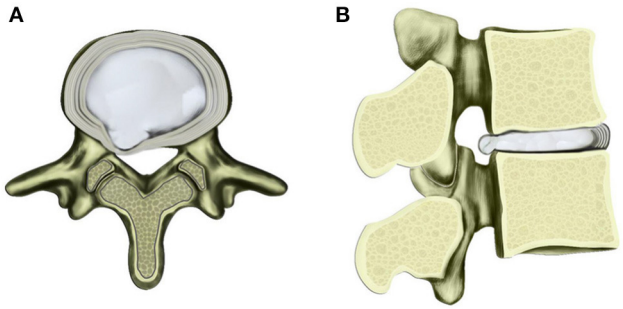


**FIGURE 3 |** Schematic diagram of contained herniated lumbar disc with transverse **(A)** and sagittal views **(B)**. Under multiple factors, the nucleus pulposus protrudes toward posterior and lateral direction with AF fibers ruptured to a certain extent.

is influenced by multiple factors. Not only the relief of the mechanical compression but also the decreased severity of the inflammatory or chemical irritation contribute to the alleviation of the clinical symptoms (46).

## Autoimmune Response and Inflammation Cascade Underlying the Spontaneous Resorption of Herniated Intervertebral Discs

Human intervertebral discs, particularly NP, belong to immune-privileged sites. The initial immune-privileged scenarios change dramatically when NP protrudes out from the closed niche (**Figure 3**). The herniated tissue is recognized as a foreign antigen by the autoimmune system, attracting immune cells and auto-antibodies, triggering an autoimmune response, and inflammation cascade (47).

In 1965, Bobechko and Hirsh revealed that an autoimmune response is induced when NP of rabbits is exposed to the systemic circulation, giving rise to the auto-antibodies production in lymph nodes (48). Subsequently, a high level of IgG and IgM was found in herniated human intervertebral discs (49, 50). Satoh et al. indicated that the antigen-antibody complexes exist particularly in the pericellular space of NP cells rather than the NP cell membrane. This implied that the newly produced substances are surrounding the NP cell, such as polysaccharides, are playing roles of auto-antigen in the immune response (51). Later, evidence of several studies suggested that not only humoral immune response but cellular immune response also exists in the autoimmune response to the herniated substance. Geiss et al. reported that activated T and B cells infiltration is observed in autologous porcine NP exposed to the autoimmune system (52), including IL-4-producing Th2 cells, which participate in the humoral immune system response (53). By using the immunohistochemical analyses, Ikeda et al. (54) and Park et al. (55) found that a small number of T cells and many macrophages are infiltrating the herniated NP tissue. Murai et al. indicated that macrophages and NK cells are the early immune responder after the exposure, then are the T and B cells (56).

Neovascularization has been widely reported contributing to the resorption mechanism. With many newly formed vessels around the disc fragments, granulation tissue was observed on the herniated NP tissue (57). Several inflammatory factors or cytokines, such as tumor necrosis factor–α, midkine, vascular endothelial growth factor, and fibroblast growth factor 2, have been identified as the inducer of angiogenesis (45, 58–62). Macrophages migrate through the newly formed vessels and converge around the disc fragments (58, 63, 64). The infiltrating macrophages produce high levels of matrix metalloproteinase (MMP), including MMP-3 and MMP-7 (65). Cells from herniated discs undergo autoself-induced apoptosis progress *via* autocrine or paracrine Fas-FasL mechanisms (55). A high level of matrix enzyme degrades the aggrecan and collagen in the herniated material. Finally, the fragment of the tissue and apoptotic cells is absorbed by the macrophages and disc cells *via* phagocytosis (65–67).

## The Hypothesis of the Spontaneous Regression in LDH Natural History

There are three hypotheses to explain the mechanism of spontaneous resorption in LDH. The first hypothesis is the dehydration and shrinkage of the herniated material (68). The second mechanism is supposed that the herniated disc, which is elastic and not separated from the main part in the intervertebral disc space, retracts back to the central place gradually (69). The third is the mechanism mentioned in the previous segment. The herniated disc is identified as a foreign antigen, inducing an autoimmune response and inflammatory cascade. Then, the matrix substance and apoptotic cells are degraded and absorbed

by the macrophages *via* phagocytosis (52). It is supposed that all of the three mechanisms contribute to the spontaneous resorption process (70).

## NON-SURGICAL TREATMENT—THE FOREMOST OPTION FOR LDH PATIENTS WITHOUT SERIOUS SYMPTOMS

LDH is treated with surgical or non-surgical measures. Non-surgical treatments of LDH include various methods, such as bed rest, lumbar supports, physical therapy, spinal manipulation, oral analgesics, muscle relaxants, epidural steroid injections, and behavioral therapy (71). Except for the presence of cauda equina syndrome and neurologic impairment, controversy still exists regarding the indications for surgical intervention. North American Spine Society's (NASS) clinical guideline for LDH with radiculopathy indicated that the evidence in a recommendation for urgent surgery is insufficient for LDH patients with motor deficits (72). Several prospective controlled studies suggested that patients undergoing non-surgical treatment should only switch to surgical treatment with exacerbated symptoms (73, 74). Either surgical or conservative measures are suggested effective both in the short and long term for patients with less severe symptoms (72). The recommendation of Danish national clinical guidelines of recent onset lumbar nerve root compression advised at least 12 weeks of a conservative treatment to LDH patients before being considered for operation unless ongoing severe symptoms such as severe pain and disability (75). However, the North American Spine Society's (NASS) clinical guideline for LDH with radiculopathy suggested that LDH patients whose symptoms are severe enough to warrant surgery seek surgical intervention in 6 months. They indicated that earlier surgery (within 6 months to 1 year) is related to faster recovery and better long-term outcomes (72).

Although surgery is effective for LDH patients with radiculopathy in the short term, the surgical complication, repeat operation, and symptomatic recurrent LDH are unavoidable frustrating issues for part of them. A meta-analysis including 34,639 surgical cases of LDH revealed that the overall incidence of complications is 2.7%, while 2.1% of the patients had repeat operations within 3 months (76). Consistently, another study conducted in the US revealed that the average reoperation rate for LDH patients is 1.9% at 90 days, 6.4% at 1 year, and 13.8% at 4 years. Decompressions without fusion account for the majority of re-operative procedures (73%), while fusion with or without decompression nearly makes up for the rest (25.7%) (77). Apart from the undesirable operational effect, symptomatic recurrent LDH is another cause of reoperation. A small part of patients (5–15%) experience unfavorable events, and 4% to 6% undergo surgery in 2 years (78–81).

Although the surgical intervention has the advantages, i.e., rapid relief of symptoms and faster recovery of neurological deficits in the short term (13), several randomized controlled trials (RCTs) showed that the difference between conservative and surgical treatment in LDH patients with radiculopathy is non-significant 1 year later after diagnosis (82). Considering that spontaneous resorption of herniated discs commonly exists in the natural history of LDH, symptoms in a proportion of the patients will resolve on their own. Parts of the patients with LDH, particularly those without serious symptoms, are likely to benefit from the conservative treatment. Part of the patients' clinical symptoms will be alleviated or even completely disappear in a short time (83). Therefore, we suggested that non-surgical treatment is the foremost recommended measure for LDH patients without serious symptoms, such as cauda equina syndrome and motor deficits, which may achieve the same clinical outcomes and avoid various discomfort caused by the operation.

### A Long-Term Complication of Lumbar Fusion

In the US, the annual incidence of spinal fusion surgeries has increased over 600% from the 1990s to 2011. Nowadays, 450 000 spinal fusion cases are performed yearly (84). The national trend has been persistent during different observational periods (85). Whereas, spinal fusion with instrumentation increases healthcare expenditures, a surge of serious complications associated with the fusion has been observed as well. Increased local stress and compensatory motion on the non-operated adjacent levels after fusion procedure were both reported, giving rise to many problems, such as adjacent segment diseases (ASD) (86).

### Adjacent Segment Disease

ASD was defined as presenting a new clinical symptomatic degenerative disease corresponding to an adjacent level following spinal fusion at an index segment (87). ASD was represented by a series of pathological changes at the adjacent segments, such as disc height loss, disc herniation, canal stenosis, osteophyte formation, spondylolisthesis, and scoliosis (88). The incidence of ASD has been reported to vary from 4 to 45.7% of patients undergoing mono-segmental and multi-level fusion (88–91). Strikingly, multiple-repeated ASD following posterior lumbar interbody fusion of a single segment has been reported (92). Four patients among 1,112 consecutive patients developed multiple-repeated ASD with multiple repeated surgeries, even fusion upper to T1.

The etiology, incidence rate, and treatment strategies for ASD remain undefined. Risk factors of ASD include obesity, natural degeneration with aging, increased stress in intra-disc, preoperative disc degeneration, intraoperative superior facet joint violation, fusion at more than four levels, adjacent cranial segment, the upper shift of lumbar motion center, and decreased sacral slope (87, 88, 93–95). The incidence rate of ASD varies in terms of studied patient samples, follow-up time frame, the number of fusion segments, fusion techniques (180 or 360 degrees), and patients' age (87, 94). Regarding treatment strategies, a systematic review and meta-analysis indicated little available evidence addressing the optimal treatment options for patients with ASD for stenosis with or without instability (96).

Adjacent segment degeneration in the radiograph is the initial stage of ASD, referring to the degeneration of adjacent levels in diagnostic imaging (such as MRI) without clinical symptoms. Several researchers investigated the prevalence of radiographic adjacent segment degeneration and reported that the incidence is ranged from 9 to 27% in the lumbar spine (97, 98). A considerable proportion of the patients underwent an additional operation in the next few years. A series of risk factors were revealed in the published paper for the adjacent segment degeneration, which is similar to ASD (99). A systematic review indicated that the difference among the fusion procedures results in the variation of incidence in adjacent segment degeneration (99). Both aspects have been suggested as the key factors to avoid adjacent segment degeneration, including the reservation of posterior elements in the fusion procedure and perioperative treatment of osteoporosis.

## Other Complications Associated With Fusion Surgery

A systematic review of the literature of lumbar fusion for degenerative disorders, including 160 studies, revealed that the overall complication rate of lumbar fusion procedure is 14% (100). Apart from ASD, other long-term complications associated with fusion surgery, such as pseudarthrosis, implant failure, and sagittal spinal imbalance, were also widely reported in the literature (101, 102). The overall fusion rate for patients undergoing lumbar fusion procedures was reported as 88.5% (100). Smoking, metabolic disorders, surgical instrumentation and technique, and fusion location have been demonstrated as the risk factors for pseudarthrosis (103, 104). In addition to this, osteopenia and osteoporosis have been suggested as another risk factor for pseudarthrosis, and implant failure, such as screw loosening (105, 106). Post-operative back pain was reported in the patients undergoing lumbar fusion procedures. In-depth investigation showed that poor post-operative spinal sagittal alignment is related to prolonged back pain (107). Apart from that, the sagittal spinal imbalance was also associated with the body imbalance, which induces falls (108). The causes of sagittal imbalance are multifactorial, including pseudarthrosis at the lumbosacral junction, adjacent segment disease, and high pelvic incidence (109). The restoration or correction of sagittal alignment is important to the patients' surgical outcome and quality of life.

# METALLOSIS ISSUE

## Metal Debris and Elevated ion Level in Arthroplasty

Due to electrochemical corrosion and/or mechanical wear, surgical metallic implants have gained increasing attention in recent years. As early as 1973, Coleman et al. (110) presented the first line of evidence on a raised level of cobalt and chromium in the blood and urine of patients with metallic total hip replacements. Submicrometer metal particles within macrophages in the liver and/or the spleen were observed in patients undergoing primary and revision total hip arthroplasty (111).

The elevated level of systemic metal particles accumulating in the end organs, such as the heart (112), liver (111), and spleen (111), resulting in systemic metal toxicity, such as cobalt toxicity (113–116), even causing death (117). Apart from that, intracellular phagocytosis of particulate debris by macrophages can trigger the release of proinflammatory cytokines in the surrounding tissue, inducing aseptic fibrosis, local necrosis, or loosening of a device secondary to metal corrosion (118). Such type of metal debris staining complication is termed metallosis (119). Metallosis is a potentially fatal complication originally found in patients after arthroplasty, which is generally associated with metal or non-metallic implant wear (120). By analyzing whole blood metal and ion levels in 185 patients undergoing bilateral Birmingham Hip Resurfacing, Matharu et al. (121) proposed that the optimal threshold was 5.5 μg/L for distinguishing patients with and without adverse reactions metal debris.

## Systemic and Local Reactions Related to Spinal Metallic Implants

Joint prostheses and spinal instrumentation have different biomechanical effects on the human body. Regardless of corrosion mechanisms, mechanical wear is the predominating reason for the metallosis after arthroplasty, whereas fretting wear is the primary cause for metallosis after spinal instrumentation (119). It is generally speculated that the inevitable micromotion at the metal-metal junctions may lead to fretting corrosion and production of the particulate metallic debris after spinal instrumentation. Spinal metallic implants are currently made of titanium alloy, containing 90% titanium, 6% aluminum, and 4% vanadium. Other metal components exist in spinal implants containing niobium. It is widely reported that Ti6Al4V is highly susceptible to fretting corrosion due to a mixed microstructure when the titania passivation layer is disrupted (122). In contrast to these findings, a long-term test showed that the titanium and cobalt chrome constructs are more resistant to fretting corrosion than stainless steel (123).

In 1999, Wang et al. (124) reported that wear debris is generated in the tissue surrounding titanium spinal implants from nine patients undergoing prior lumbar decompression and fusion procedure and reoperation. Metal levels were higher in patients with pseudarthrosis than patients with a solid spinal fusion (30.36 μg/g of dry tissue vs. 0.586 μg/g of dry tissue). In 2003, Kaisai et al. (125) studied metal concentrations in the serum and hair of 46 patients with titanium alloy spinal implants, using inductively coupled plasma emission spectroscopy. Accordingly, they noted that one-third of involved patients exhibited higher serum or hair metal concentrations following surgery. Titanium or aluminum may have distant organ accumulation from the spinal implants. In 2008, Richardson et al. (126) reported higher serum titanium levels in 30 patients with titanium alloy spinal instrumentation prospectively in comparison with controls (2.6 vs. 0.71 μg/L), using high resolution inductively coupled plasma-mass spectrometry [HR-ICP-MS, detection limit

for titanium as 0.25 μg/L (ppm)]. Instrumented spinal fusion can result in abnormally elevated serum titanium, aluminum, and niobium levels in pediatric patients undergoing instrumented spinal arthrodesis to correct scoliosis and kyphosis (127–129). A systematic review concerning the concentration of metal ions following multi-level spinal fusion, which includes 18 studies and encompasses 653 patients, showed that metal ions are elevated after instrumented spinal fusion, notably Cr levels from stainless steel implants, and Ti from titanium implants (130). Moreover, serum metal ion levels correlate positively with fusion segments and numbers of spinal implants.

### The Harmful Effect of Metallosis After Spinal Implantation

Accumulating evidence has unraveled local and systemic reactions to metal spinal implants. Metal particulate debris deposited in the soft tissue surrounding spinal implants was shown to activate a macrophage response that triggers the release of proinflammatory cytokines, leading to mild chronic inflammation, and stimulating the formation of the metal debris granuloma (131). The chronic inflammation irritated by the metal debris was suggested to be associated with the late operative site pain, which is eliminated until the implant is removed (132). Several researchers reported that the intraspinal extradural granuloma resulting from the foreign body reaction to the metallic wear debris contributes to the compression of the neurological elements and neurological symptoms mimicking the lumbar spinal stenosis (133–135). Moreover, metal debris has been shown to induce the mature osteoclast precursor and apoptosis of osteoblast, increase the peri-prosthetic bone resorption, and inhibit osteogenesis. These effects result in implant debris-related osteolysis, aseptic fibrosis, local necrosis, or implant loosening (136–140).

Metal debris has also been displayed to stimulate the immune system to induce a series of type IV delayed-type IV hypersensitivity responses (141, 142). These immunogenic reactions are presented as anorexia, fatigue (143), severe dermatitis (144), urticarial (145), and vasculitis (145). In addition, much evidence indicates that degraded metal particles from spinal metallic implants can enter the systemic blood circulation and deposit in the heart, liver, and spleen. The average level of serum titanium is similar to that of patients undergoing arthroplasty. Although a few findings have been reported, the long-term impact of elevated serum metal concentrations on patients with a spinal implant is not entirely clear. Furthermore, there has been no established threshold above which metal concentrations will be toxic after the spinal instrumented surgery. Removing the spinal implantation at the right time may be a method to avoid metallosis.

## SPINAL IMPLANT REMOVAL

The latest updated guidelines (NG59) drafted by the National Institute for Health and Care Excellence in the UK (https://www.nice.org.uk/guidance/ng59) states that fusion for non-specific low back pain should be strictly used only for RCTs (146). The guidelines reflect those lessons obtained from clinical practice and reports. There have been no established indications for spinal implant removal until now. Therefore, whether to proceed depends on the surgeon's preference.

Even though the application of spinal instrumentation increased the probability of successful spinal fusion, stress shielding induced osteoporosis on account of the rigid fixation and increased the risk of recurrent fracture after implant removal (106, 147, 148). Acquired spondylolysis has been a well-recognized stress fracture after posterior lumbar fusion since 1963 (149). Nevertheless, adverse events have been reported following pedicle screw constructs removal, including pedicle stress fracture due to iatrogenic weakness of the pedicles following removal (150, 151), vertebral compression fracture within a solid lumbar fusion mass (152), or recurrent vertebral fracture following pedicle screw removal for index burst fracture (153). Therefore, the surgeon should attach attention to the implant removal time and method, avoiding implant removal failure.

## OTHER CHALLENGES

Besides those mentioned above existing challenging issues, there are other questions to be solved, including decreased quality of life due to lumbar rigidity radiation exposure from perioperative and follow-up diagnostic imaging. In addition to common clinical outcome measures for lumbar spine surgery, indicators have been noted reflecting lumbar rigidity due to the decrease in kinematic units following lumbar fusion. Sciubba et al. (154) evaluated the impact of stiffness on activities of daily living following instrumented total lumbar fusion. The most affected activities of daily living included dressing or bathing the lower half of the body and performing personal hygiene functions after toileting.

By adding instrumentation, patients have to experience additional ionizing radiation exposure for the orientation of pedicle screws during surgery with fluoroscopy (155–157) observations on repeated radiographs for clinical outcome follow-up. Compared to pure decompression, adding instrumentation will result in more cumulative radiation exposure for surgeons, medical staff in operating theaters, and patients. Importantly, the awareness of such potential harms is low amongst medical professionals (158) and patients (159, 160).

Residual and recurring back pain after surgery is common in LDH surgeries. The proportion of patients reporting short-term (6–24 months) and long-term (>24 months) recurrent back pain ranged from 3–34% to 5–36%, respectively in a systematic literature review (79). Some people who have persistent pain postoperative are still unclear (161). Severe endplate changes, such as endplate avulsion, damaged the lumbar stability and maybe resulted in a higher recurrence rate and residual back pain (162, 163). LBP has been suggested to be associated with postural and structural asymmetries. CEP degeneration accompanied by loss of cellularity results in the asymmetric loading of the lumbar spine in LDH. Fusion surgery provides the stabilization and maybe correct asymmetry of the lumbar spine in part (164). However, the current operation aims not to solve the imbalance of load, nor can it completely

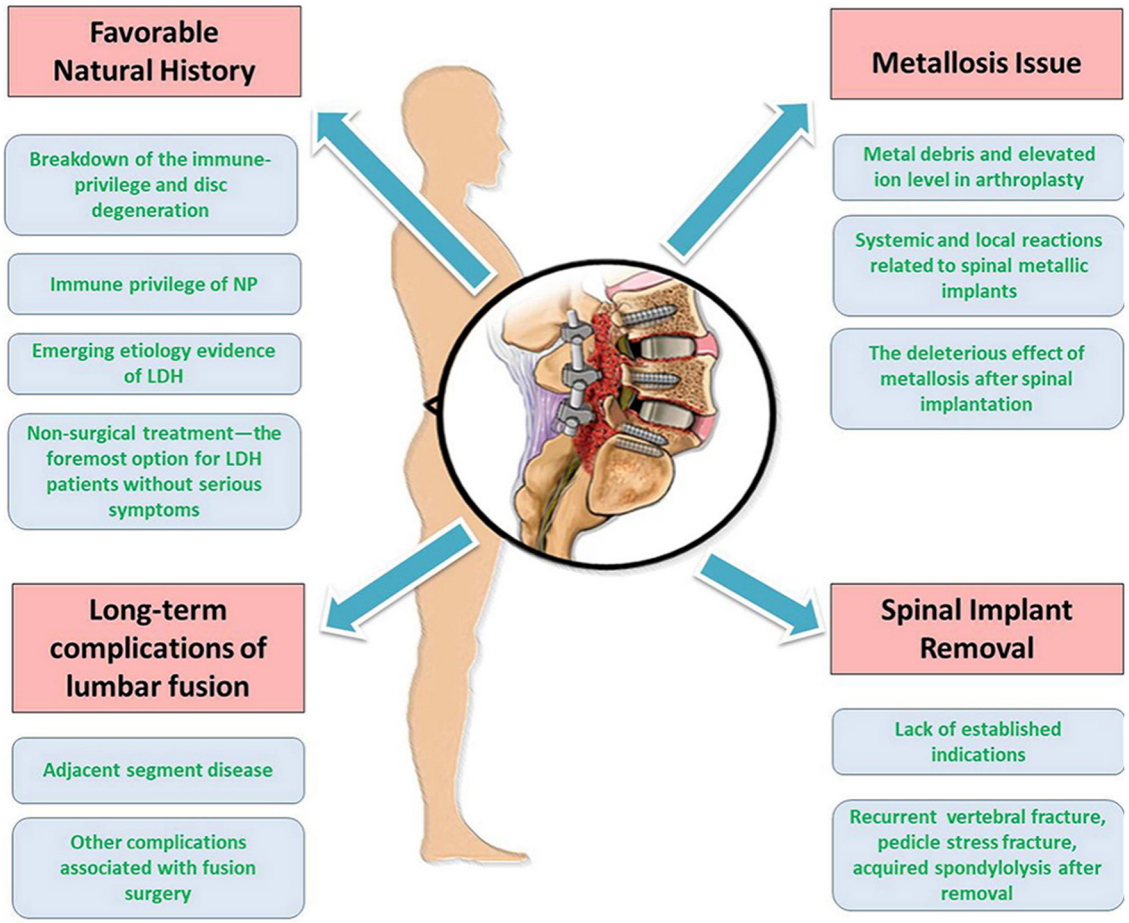


**FIGURE 4 |** Summarizations of the different aspects of the review. There are tetrad critical issues pertaining to surgical treatment of LDH, i.e., favorable natural history, long-term complications of lumbar fusion, metallosis issue, and spinal implant removal.

solve the problem. Asymmetry of lumbar loading may still be one of the causes of residual back pain postoperative. The predictors of residual LBP after decompression included more severe LBP at baseline, degenerative scoliosis, and Cobb angle size (165).

As the second most mobile part of the human axis, the lumbar spine and related LDH have been a hot topic for the medical community (164). Nevertheless, LBP, most commonly caused by a herniated disc, is a constant concern (166). For decades, lumbar discectomy has been done by neurosurgeons as the general surgical practice to solve the disease (167, 168). The discovery of X-Ray brought about a shift of paradigm in the practice of neurosurgery (169). The introduction of microsurgical techniques led to an essential evolution in lumbar disc surgery (170). For those who have failed conservative treatment, surgery is the only option that must be considered. However, while the operation solves the symptoms, it also brings problems that can not be ignored. This paper summarizes the cons of surgical treatment from different perspectives. These summaries are useful supplements to the present literature, providing a unique vision for surgeons and patients who attempt to choose surgical treatment.

## CONCLUSIONS

Due to various triggering factors, lumbar surgeries with or without implementation increase rapidly with great health expenditures. In the review, we analyzed the tetrad critical issues about surgical intervention for LDH, i.e., favorable natural history, long-term complication of lumbar fusion, metallosis, and implant removal (**Figure 4**). Based on the limited evidence available so far, lumbar surgery solves the symptoms for the patients with LDH and brings a new series of unexpected problems. Therefore, the long-term effects of surgery should be closely observed. Surgical decisions should be made prudently for each patient.

## AUTHOR CONTRIBUTIONS

HW conceived the study. ZW, HS, and TL investigated and retrieved the published papers, as well as wrote

the original draft. FS, JZ, ZL, and KM reviewed and edited the final version of the manuscript. All authors have read and agreed to the final version of the manuscript.

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# Research Hotspots and Trends Analysis of Patellar Instability: A Bibliometric Analysis from 2001 to 2021

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**Background:** Patellar instability is a common multifactorial disease in orthopedics, which seriously affects the quality of life. Because of the unified pathogeny, diagnosis and treatment, patellar instability has gradually attracted the interest of more scholars these years, resulting in an explosive growth in the research output. This study aims to summarize the knowledge structure and development trend in the field from the perspective of bibliometrics.

**Methods:** The data of articles and reviews on patellar instability was extracted from the Web of Science database. The Microsoft Excel, R-bibliometrix, CiteSpace, VOSviewer, Pajek software are comprehensively used to scientifically analyze the data quantitatively and qualitatively.

**Results:** Totally, 2,155 papers were identified, mainly from North America, Western Europe and East Asia. Until December 31, 2021, the United States has contributed the most articles (1,828) and the highest total citations (17,931). Hospital for Special Surgery and professor Andrew A Amis are the most prolific institutions and the most influential authors respectively. Through the analysis of citations and keywords based on a large number of literatures, "medial patellofemoral ligament construction", "tibial tubercle-trochlear groove (TT-TG) distance", "epidemiological prevalence", "multifactor analysis of etiology, clinical outcome and radiographic landmarks " were identified to be the most promising research directions.

**Conclusions:** This is the first bibliometric study to comprehensively summarize the research trend and development of patellar instability. The result of our research provides the updated perspective for scholars to understand the key information in this field, and promote future research to a great extent.

**Keywords: Bibliometrics, visualized study, patellar instability, patellofemoral joint, patellar dislocation**

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## INTRODUCTION

Knee joint is the largest compound joint in human body. Patellofemoral instability as a common disease in orthopedics and the main cause of anterior knee pain syndrome, especially in young people, often leads to patellar dislocation or subluxation, which brings great pain to patients (1). The multiply risk factors leading to patellar instability include the dysplasia of patellar and

trochlear osseous structure, the integrity and balance of periarticular ligaments, the systemic conditions affecting connective tissue, and the overall muscle strength, which also complicate the diagnosis and analysis of patellar instability (2). Patellar dislocation leads to pain, decreased mobility, osteochondral fractures, and patellofemoral arthritis (3). The complexity of the pathogenesis also leads to the diversity of treatment methods, and there is no unified opinion on the choice of conservative or surgical treatment, as well as on the choice of surgical procedure (4).

In view of the above aspects, patellofemoral instability has attracted more and more attention of researchers, and a large number of relevant studies have been published. However, the rapidly increasing number of publications makes it increasingly difficult for researchers to keep up with the latest findings, even in their professional field (5). Although the emerging systematic evaluation and meta-analysis can provide researchers with more ideas, these articles only focus on some specific aspect (4, 6). Some meaningful information, such as the number of publications, the collaboration of countries, institutions and authors, and the scientific analysis of research hotspots, prediction of hotspots are not included (7).

Bibliometrics based on scientific statistical methods can reliably identify and analyze the above information, so as to identify global trends and build knowledge structure, which is not only beneficial to novice researchers, but also to the experts (8). Bibliometric analysis has been applied in medical field, exerting a great impact in Orthopedics (9), Psychiatry (10, 11), Urology (12) and other fields.

As shown in **Figure 1**, our analysis mainly contains five aspects. Firstly, we analyze the growth trend of the number of publications. Then we analyze the most productive countries, institutions and researchers, which helps researchers find the most suitable research institutions or scholars to cooperate. Then there is the analysis of journals, including journal co-citation analysis and the dual-map overlay visualization, which helps researchers find the most suitable journals for study and submission. The most prominent part of our research is the analysis of references and keywords. We conduct main path analysis and co-citation cluster analysis on references, which are helpful to clarify the development process and research progress in this field. The co-occurrence analysis of keywords identifies the relationship between various research directions in this field. In addition, we use multiple analysis software to comprehensively analyze keywords to identify the research frontiers and development directions in this field, which may inspire researchers and guide researchers to make more breakthroughs in these promising directions.

## REVIEW ON PREVIOUS LITERATURE

In order to avoid duplicated and unnecessary investment of research funds and time, the researchers independently and systematically reviewed the Clarivate Analytics Web of Science (WOS) database on the last day of 2021, that is, December 31, 2021. The WOS database is the selected collection of high-quality academic peer-reviewed literatures. We found that in the research field of patellar instability, no bibliometric articles

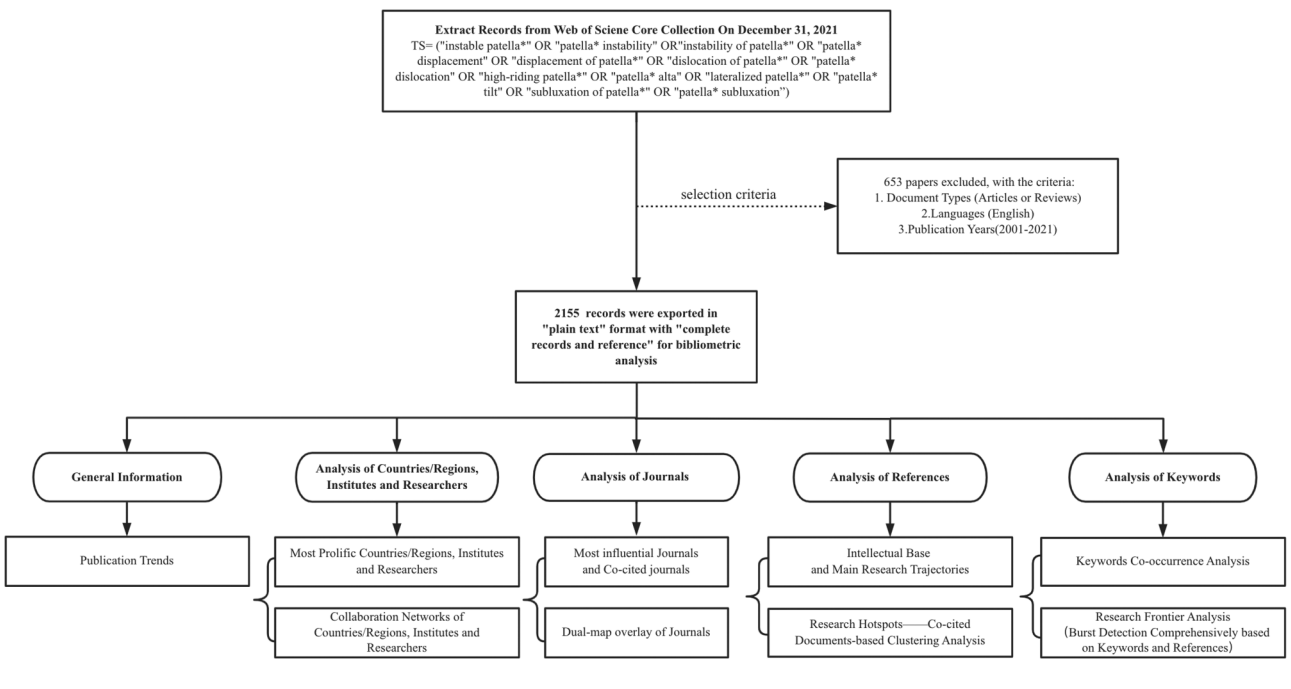


**FIGURE 1** | The work flow diagram.

have been published. Bibliometrics makes quantitative analysis of publications based on mathematical and statistical methods. It can scientifically make use of data extracted from articles to analyze and visualize the research hotspots and research frontiers in the identified research domains, which may greatly promote the development of the research field.

## MATERIALS AND METHODS

The Science Citation Index Expanded (SCI-Expanded) of the Clarivate Analytics Web of Science Core Collection (WoSCC) was the most commonly used scientific information source for bibliometric analysis (13). We had carefully formulated the retrieval plan and selected the last day of 2021 for information screening and extraction, so as to ensure the integrity of the latest research information in 2021 to the greatest extent and avoid the information bias caused by the daily update of the database. The specific search formula was as follows: TS = ("instable patella*" OR "patella* instability" OR "instability of patella*" OR "patella* displacement" OR "displacement of patella*" OR "dislocation of patella*" OR "patella* dislocation" OR "high-riding patella*" OR "patella* alta" OR "lateralized patella*" OR "patella* tilt" OR "subluxation of patella*" OR "patella* subluxation"). The search timespan was set as 2001–2021. We only included two types of literature: original articles and reviews, which had standard references and had been strictly reviewed by experts in the same field. Finally, 2,155 records were finally retrieved. Then we exported records in "plain text" format with "complete records and reference".

## DATA ANALYSIS AND DESCRIPTIVE ANALYSIS

In total, we mainly used 5 scientometric software and Microsoft Excel program to perform bibliometric analysis (**Figure 1**) (14).

R-bibliometrix software package based on R-Studio (version3.0.3, http://www.bibliometrix.org) (15), VOSviewer software (version1.6.16, https://www.vosviewer.com/download) (16), CiteSpace software (version5.7R5W, https://citespace.podia.com/courses/download) (17), Hiscite software (https://histcite.updatestar.com/) (18) and Pajek software (http://vlado.fmf.unilj.si/pub/networks/pajek/) (19) were employed by the researchers to perform bibliometric analysis.

The VOSviewer software developed by Professor van Eck and Waltman and the CiteSpace software developed by Professor Chen are highly reliable and practical bibliometric software mainly used to visualize and analyze the knowledge structure and the evolution trend of scientific literature in a certain field (20). Besides, Citespace and VOSviewer can extract sub-clusters from the overall structure of literature network through clustering analysis to identify research subdomains, namely research hotspots (21, 22). Nodes in the figures represent countries, institutions, authors, journals, citations or keywords, and links between nodes represent collaboration, co-occurrence or co-citation relationships. We set the nodes in the figures generated as the rainbow ring diagram pattern. The center color of each rainbow node represents the year the study published, and the outer colors represents the years the literature highly cited. The flow of knowledge can be seen from the change of colors in nodes, links and clusters. The warmer the color, the later the year.

In addition, we employed the R-bibliometrix, VOSviewer and CiteSpace software for overlapping analysis to identify the research frontier, which can to a great extent predict the research directions that may produce significant breakthroughs in the next few years. Hiscite and Pajek software are integrated to extract main research trajectories from the huge literature citation network (19, 23). Through in-depth review of the result, researchers can quickly grasp the knowledge base and development trend in the field, so as to improve their own research results and adjust their own research strategies.

## RESULTS AND DISCUSSION

### Publication Trends

Accessibility to Web of Science, one of the largest citation databases in the world, was obtained through Peking University library. Totally, 2,155 documents related to patellar instability were retrieved. As is demonstrated in **Figure 2**, the research output before 2001 was relatively low. Despite the appearance of the volatility to decrease at some special time points, we can find a gradually increasing trend year by year after 2001 and the output entered an outbreak growth stage after 2015. Through polynomial fitting analysis between the publication year and the number of publications, we found that there existed a significant correlation (the coefficients of determination ($R^2$) were 0.9397, 0.9329, and 0.8173 for total documents, articles, and reviews, respectively). According to polynomial fitting analysis, we predicted that the number of papers published in 2025 will reach approximately 270, including about 235 original papers and 35 reviews. In general, the vigorous development of orthopedics and sports medicine makes the research more and more in-depth. However, it can be found that although the number of published publications increases year by year, high-quality RCT researches are still relatively lacking.

## ACTIVE COUNTRIES/REGIONS, INSTITUTES AND RESEARCHERS

As is shown in **Table 1**, the most productive countries and institutions are mainly located in North America, Europe and East Asia. The top 5 influential countries are the United States, Germany, the United Kingdom, Japan and France. In this field, the United States has a pivotal impact, yielding a total of 17,931 citations, far exceeding that of other countries. **Figures 3A,B** display the international cooperation among different countries worldwide. The Citespace setting parameters of **Figure 3A** were as follows: # Years Per Slice = 1,

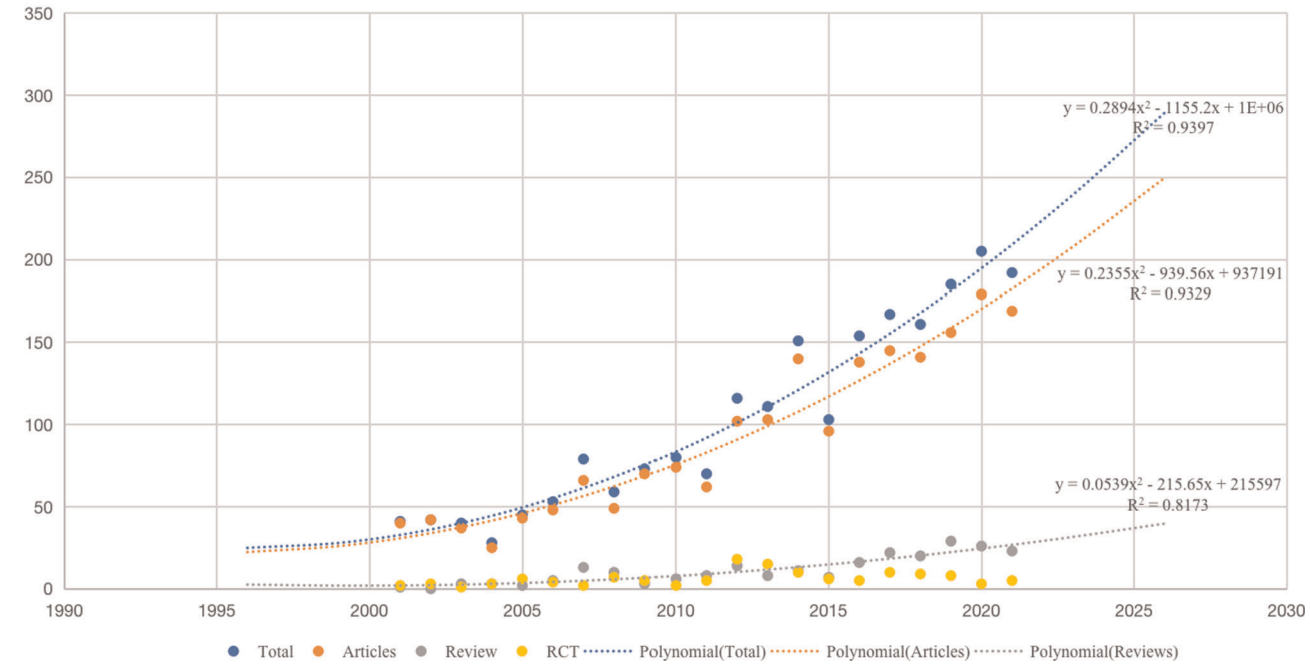


**FIGURE 2** | Trends in publications from WOS (2001–2021) by year in the field of patellar instability and the corresponding polynomial fitted curves.

**TABLE 1** | The top 15 influential countries and prolific institutions.

| Rank | Country | Total Citation | Average Article Citations | Number of Documents | Affiliations | Articles |
|---|---|---|---|---|---|---|
| 1 | USA | 17,931 | 25.54 | 795 | Hosp Special Surg | 86 |
| 2 | Germany | 4,930 | 28.66 | 212 | Hebei Med Univ | 83 |
| 3 | UK | 4,336 | 27.44 | 185 | Univ Minnesota | 48 |
| 4 | Japan | 2,388 | 20.07 | 128 | Johns Hopkins Univ | 46 |
| 5 | France | 1,902 | 23.48 | 109 | Tech Univ Munich | 37 |
| 6 | China | 1,867 | 8.45 | 205 | Stanford Univ | 34 |
| 7 | Switzerland | 1,784 | 25.13 | 113 | Univ Zurich | 34 |
| 8 | Finland | 1,229 | 45.52 | 32 | Mayo Clin | 33 |
| 9 | Canada | 1,025 | 19.71 | 79 | Ohio State Univ | 31 |
| 10 | Netherlands | 969 | 22.53 | 51 | Univ Sao Paulo | 31 |
| 11 | Denmark | 860 | 45.26 | 20 | Norfolk and Norwich Univ Hosp | 30 |
| 12 | Australia | 830 | 23.06 | 62 | Med Univ Innsbruck | 29 |
| 13 | Korea | 804 | 12.37 | 72 | Univ E Anglia | 29 |
| 14 | Italy | 724 | 13.92 | 78 | Univ London Imperial Coll Sci Technol and Med | 28 |
| 15 | Austria | 557 | 17.41 | 49 | Univ ULM | 28 |
| 16 | Brazil | 552 | 17.81 | 41 | Harvard Med SCH | 27 |
| 17 | Spain | 491 | 21.35 | 29 | Boston Univ | 25 |
| 18 | Sweden | 435 | 39.55 | 16 | Cincinnati Childrens Hosp Med CTR | 25 |
| 19 | Turkey | 415 | 7.69 | 61 | Harvard Univ | 25 |
| 20 | Belgium | 388 | 24.25 | 24 | Rush Univ | 24 |

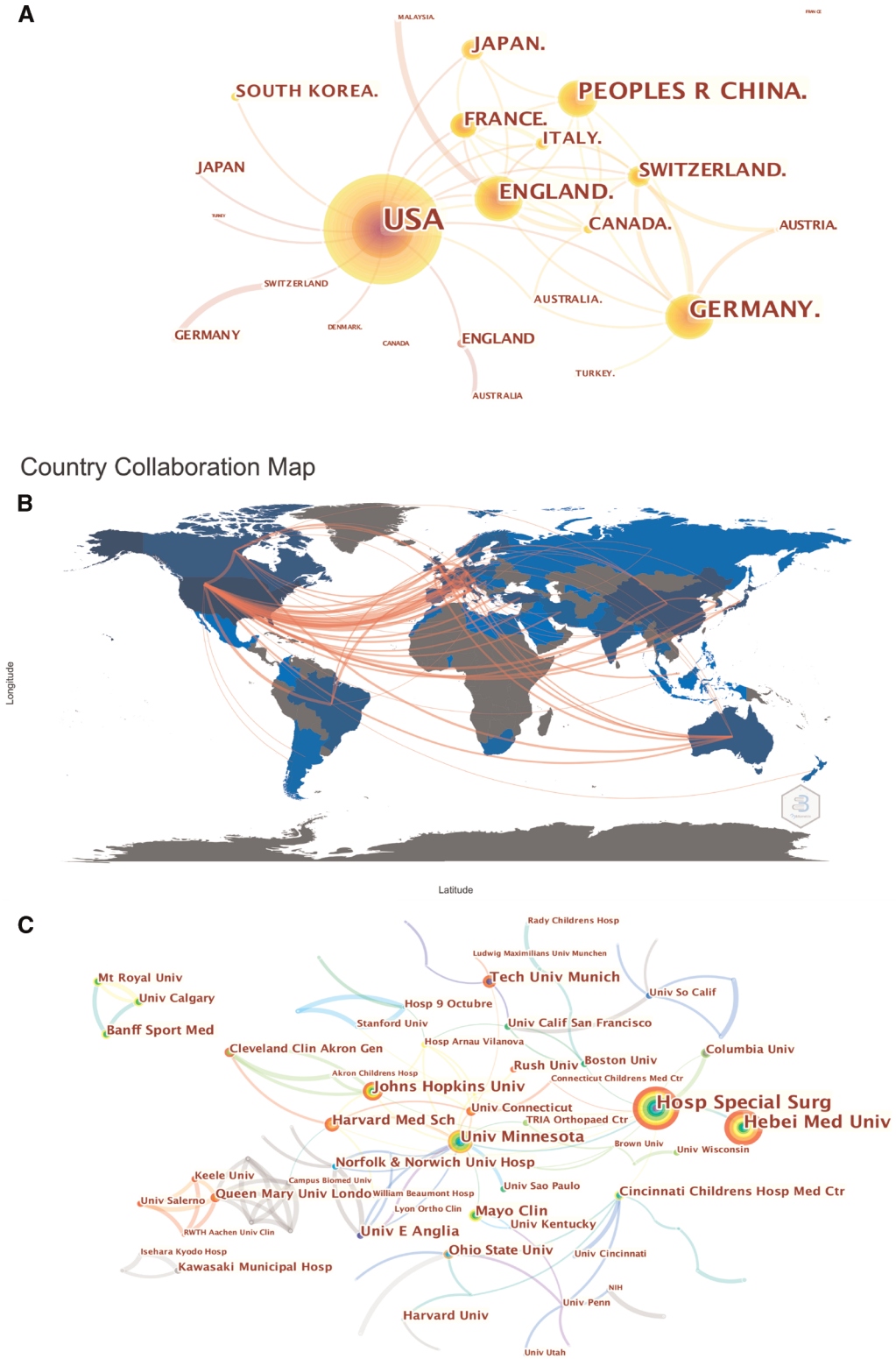


**FIGURE 3** | (**A**) The country collaboration network generated by the Citespace software. (**B**) The country collaboration plotted on the world map. (**C**) The collaboration network of institutions generated by the Citespace software.

Top *N*% = 25, pruning algorithm was adopted. The thickness of the lines between the two countries indicates the cooperation strength. It can be found that extensive cooperative relations have been established among countries in North America, Western Europe and East Asia, but the cooperation among developing countries is still weak and needs to be further strengthened. In addition, it's necessary for us to note that the average Chinese article citation is not high, whereas the average article citation of Finland is outstanding, suggesting that there is not only a need to improve the quantity but also to seek breakthroughs in the international influence of publications from emerging countries.

Most of these prolific institutions are world-renowned research institutions, with prominent positions in the history of orthopedics and sports medicine research. We can see from the **Figure 3C** that extensive cooperation between institutions has been established. The Citespace setting parameters of **Figure 3C** were as follows: # Years Per Slice = 1, Top *N*% = 5, pruning algorithm was adopted. For example, Professor Wang Fei from Hebei Medical University has formed a stable cooperative relationship with the Hospital for Special Surgery. In addition, from the color and size of the nodes, it can be seen that the top 4 prolific institutions are Special Surgery Hospital, Hebei Medical University, University of Minnesota and Harvard Medical School. Focusing on the research of these high-yield institutions and the collaboration can help researchers understand the most significant scientific advances worldwide.

Additionally, a total of 318 publications from the top 15 influential authors account for 14.76% of all publications in this field. The author with the highest total citations was Andrew A Amis with 1,586 citations, followed by Philip B Schöttle with 1,265 citations, Elizabeth A Arendt with 1,251 citations and David H Dejour with 1,120 citations. **Tables 2**, **3** shows the details of the top 15 active researchers, including their H-index (24, 25), total citations, and the relevant information of their representative articles. Collaborations among these authors and their productions over time were shown in **Figures 4A,B**, respectively. The Citespace setting parameters of **Figure 4A** were as follows: # Years Per Slice = 1, Top *N*% = 2, pruning algorithm was adopted. It can be found that there are four research clusters, which are radiated by one or two core authors, such as Fei Wang, Vicente Sanchisalfonso, Andrew J Cosgarea, Jack Farr, Elizabeth A Arendt and David Dejour. Generally speaking, the research cluster led by Fei Wang, Andrew J Cosgarea and Jack Farr has been comparatively active in recent years, while the research cluster led by Elizabeth a Arendt and David dejour had greater influence a few years ago.

It is worth noting that one of the most influential authors–Andrew A Amis is a professor from the Department of Mechanical Engineering in Imperial College London, focusing on biomechanics for orthopedics (26). The comprehensive research of medicine and engineering has gradually become the hotspots, which can make a major breakthrough that is difficult to be achieved through traditional clinical researches (27).

With David H Dejour as the representative, Lyon School stands out as one of the notable landmarks in the progress of the research of patellar instability. Through the research and summary of several generations of scholars, Lyon School had established the theory that the abnormality of bone structure is the basic cause of patellar instability, and they formulated quantitative standards for radiographic detection and surgical indications for osseous risk factors (6, 28). In the last 20 years, soft-tissue surgeries such as medial patellofemoral ligament reconstruction have gradually become the worldwide research hotspot (29), which led to the formation of the America School with soft-tissue reconstruction as their core concept. And it can be seen from **Figure 4** that Chinese scholars played an increasingly significant role in this field. For example, Professor Fei Wang made outstanding contributions in both clinical and preclinical medicine research on patellar instability.

**TABLE 2** | The top 15 influential authors.

| Rank | Author | H-index | Total citation of the Authors | Number of publications by the authors |
|---|---|---|---|---|
| 1 | Amis AA | 17 | 1,586 | 19 |
| 2 | Schottle PB | 15 | 1,265 | 15 |
| 3 | Arendt EA | 20 | 1,251 | 35 |
| 4 | Dejour D | 15 | 1,120 | 20 |
| 5 | Powers CM | 14 | 1,096 | 15 |
| 6 | Nomura E | 12 | 871 | 15 |
| 7 | Balcarek P | 12 | 820 | 23 |
| 8 | Dahm DL | 13 | 809 | 19 |
| 9 | Donell ST | 15 | 774 | 21 |
| 10 | Fucentese SF | 12 | 758 | 19 |
| 11 | Smith TO | 16 | 740 | 25 |
| 12 | Nelitz M | 12 | 738 | 17 |
| 13 | Krych AJ | 12 | 649 | 18 |
| 14 | Stuart MJ | 13 | 641 | 17 |
| 15 | Wang F | 13 | 530 | 40 |

## Journals

Scientific publications are important carriers of knowledge in a specific field. The statistical analysis of the distribution of the journal source can help researchers choose the most appropriate journals to publish their research findings, and also help the most relevant journal sources to obtain more abundant manuscript submission. The top 20 journals were presented in **Table 4**. Visualization of the journal co-citation analysis was shown in **Figure 5** (30). The journal with the largest H-index and the largest total citations is the American Journal of Sports Medicine (H-index = 58, total citations = 14,370) while the journal with the largest number of publications is Knee Surgery Sports Traumatology Arthroscopy (Number of Publications, NP = 311).

In addition to these two journals, the top ten influential journals include: Knee (NP = 134), Arthroscopy-the Journal of Arthroscopic and Related Surgery (NP = 88), Archives of Orthopaedic and Trauma Surgery (NP = 56), International

**TABLE 3** | The most influential articles by the top 15 authors.

| Rank | Author | The Most Cited Articles by Each Author | The Journals in which the Top Articles Were Published | Publication Year | Total Citation of the Article |
|---|---|---|---|---|---|
| 1 | Amis AA | Anatomy and biomechanics of the medial patellofemoral ligament | Knee | 2003 | 424 |
| 2 | Schottle PB | Radiographic landmarks for femoral tunnel placement in medial patellofemoral ligament reconstruction | American Journal of Sports Medicine | 2007 | 333 |
| 3 | Arendt EA | Current concepts of lateral patella dislocation | Clinics in Sports Medicine | 2002 | 221 |
| 4 | Dejour D | Osteotomies in patello-femoral instabilities | Sports Medicine and Arthroscopy Review | 2007 | 274 |
| 5 | Powers CM | Patellofemoral kinematics during weight-bearing and non-weight-bearing knee extension in persons with lateral subluxation of the patella: a preliminary study | journal of Orthopaedic & Sports Physical Therapy | 2003 | 199 |
| 6 | NOmura E | Long-term follow-up and knee osteoarthritis change after medial patellofemora ligament reconstruction for recurrent patellar dislocation | American Journal of Sports Medicine | 2007 | 119 |
| 7 | Balcarek P | Anatomy of lateral patellar instability trochlear dysplasia and tibial tubercle-trochlear groove distance is more pronounced in women who dislocate the patella | American Journal of Sports Medicine | 2010 | 120 |
| 8 | Dahm DL | Predictors of recurrent instability after acute patellofemoral dislocation in pediatric and adolescent patients | American Journal of Sports Medicine | 2013 | 160 |
| 9 | Donell ST | Acute patellar dislocation in children and adolescents: a randomized clinical trial | Journal of Bone and Joint Surgery-American Volume | 2008 | 240 |
| 10 | FucentesE SF | Clinical and radiological outcome of medial patellofemoral ligament reconstruction with a semitendinosus autograft for patella instability | Knee Surgery Sports Traumatology Arthroscopy | 2005 | 221 |
| 11 | Smith TO | Operative versus non-operative management of patellar dislocation. a meta-analysis | Knee Surgery Sports Traumatology Arthroscopy | 2011 | 74 |
| 12 | Nelitz M | Observer agreement on the dejour trochlear dysplasia classification a comparison of true lateral radiographs and axial magnetic resonance images | American Journal of Sports Medicine | 2012 | 120 |
| 13 | Krych AJ | CT and MRI measurements of tibial tubercle-trochlear groove distances are not equivalent in patients with patellar instability | American Journal of Sports Medicine | 2013 | 123 |
| 14 | Stuart MJ | CT and MRI measurements of tibial tubercle-trochlear groove distances are not equivalent in patients with patellar instability | American Journal of Sports Medicine | 2013 | 123 |
| 15 | Wang F | Functional bundles of the medial patellofemoral ligament | Knee Surgery Sports Traumatology Arthroscopy | 2010 | 90 |

Orthopaedics (NP = 55), Journal of Knee Surgery (NP = 55), Journal of Pediatric Orthopaedics (NP = 49), Orthopaedic Journal of Sports Medicine (NP = 49), Journal of Arthroplasty (NP = 47). Scientific achievements with major breakthroughs in the future are likely to appear in these journals.

As is shown in **Figure 6**, each point represents a journal, and the most influential journals are represented by ellipses instead - the center of the ellipses represent the subject field, the horizontal axis of the left ellipses represents the number of authors, and the vertical axis represents the number of publications. Meanwhile, the horizontal axis of the right ellipses represents the number of cited authors, and the vertical axis represents the number of times the journal has been cited. Besides, the journals are grouped into clusters by adopting the Blondel algorithm to identify the major research disciplines (31), because the citing papers are regarded as the frontiers of knowledge and the cited papers are considered as the basis of knowledge.

In addition, the colored paths between the clusters of journals in the dual-map overlay indicate the citation relationships between the citing journals and the cited journals, which demonstrate the citation trajectory and knowledge flow of knowledge (32). The colored paths indicated that studies published in Medicine/Medical/Clinical/Surgery journals usually cite the studies published in Sports/Rehabilitation/Surgery, Health/Nursing/Medicine, Molecular/Biology/Genetics and Forensic/Anatomy/Medicine. More information about the representative citing and citied journals in each cluster can be detected in **Figure 6**. For instance, the most representative journals in the Health/Nursing/ Medicine cluster are the Clinical Orthopaedics and Related Research, the Journal of Bone and Joint Surgery, the Arthroscopy, the Knee and the International Orthopeadics.

In addition, the **Figure 8C** shows the three-field plot generated by R-Bibliometrix software package, which can intuitively show the flow of knowledge - including the cooperative relationship between the most productive authors and the most productive institutions, as well as their most preferred journal sources to publish their scientific findings.

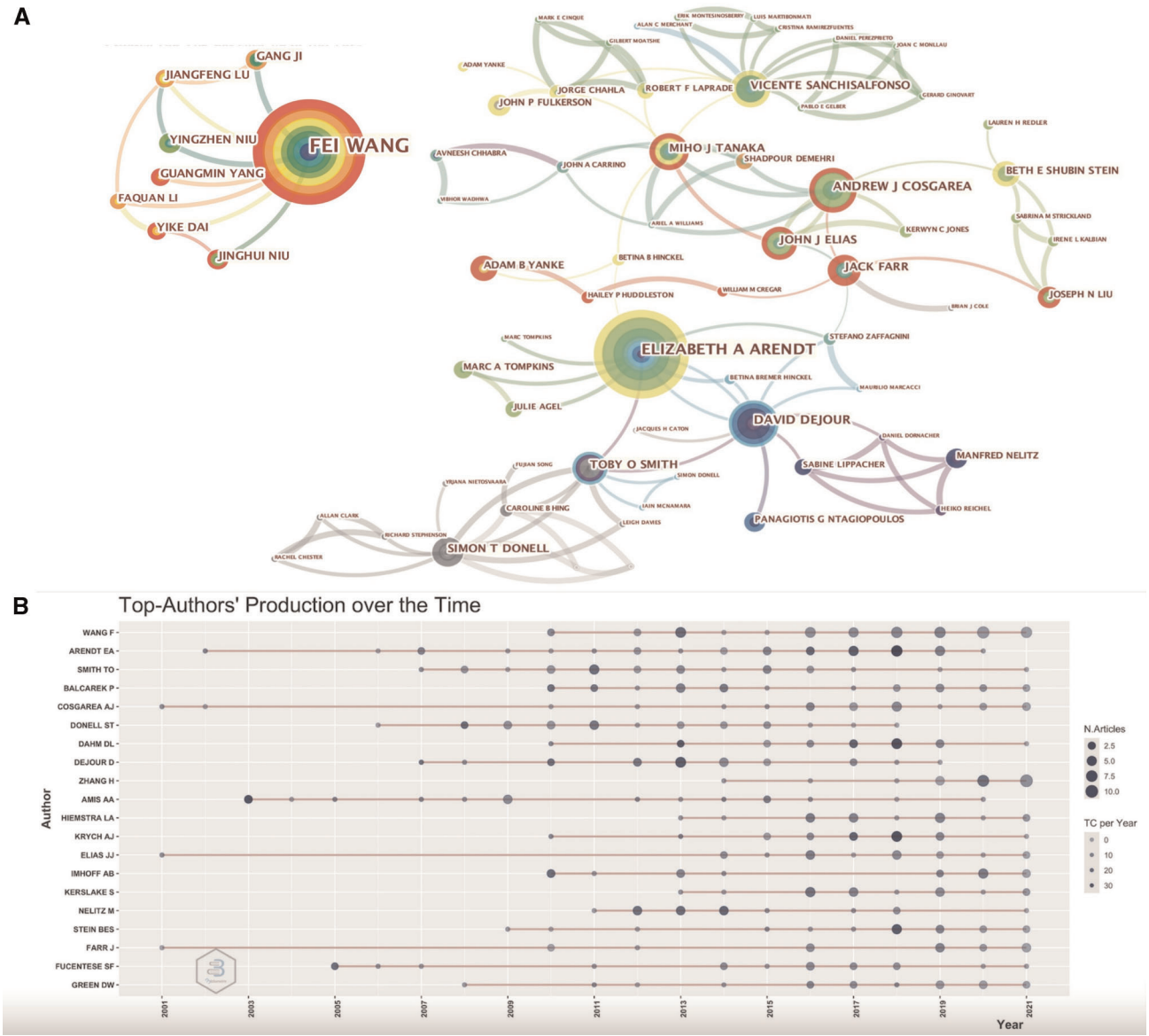


**FIGURE 4** | (**A**) The collaboration network of researchers generated by the Citespace software. (**B**) The top twenty prolific researchers in the field and their publications over time. The larger the node, the more articles published. The deeper the color, the more citations. The color represents the number of the publications, and the color represents the citations per year.

## References

Reference is one of the most significant aspects of bibliometrics. We mainly analyzed the co-citation information of the articles from two aspects (33).

### Intellectual base and main research trajectories of the patellar instability research field

Frequently cited literatures usually have great influence in the relevant research fields. As is shown in **Figure 7A**, a co-citation reference network with 105 nodes was fabricated to demonstrate the most significant studies. The selection criteria were set as follows: # Slice Length = 1 year, Top1% per slice, pruning algorithm was adopted. This reference network with a density of 0.0211 contains 21 colors from light gray to bright red representing different years. From the links, that is, the co-citation relationship, we can see the development process of the research field and the correlation between the influential literatures. Moreover, burst detection, an algorithm developed by Kleinberg (Bursty and Hierarchical Structure in Streams), was an effective analytic tool to capture the sharp increase of references or keywords popularity within a specified period (34). This function can serve as an efficient

**TABLE 4** | The most 20 prolific journals in the field.

| Rank | Source | H-index | Total Citation | Number of Publications | Quartile in category (2020) |
|---|---|---|---|---|---|
| 1 | Knee Surgery Sports Traumatology Arthroscopy | 44 | 7,314 | 311 | Q1 |
| 2 | American Journal of Sports Medicine | 55 | 8,983 | 163 | Q1 |
| 3 | Knee | 25 | 2,657 | 134 | Q3 |
| 4 | Arthroscopy-the Journal of Arthroscopic And Related Surgery | 34 | 3,499 | 88 | Q1 |
| 5 | Archives of Orthopaedic and Trauma Surgery | 16 | 979 | 56 | Q2 |
| 6 | International Orthopaedics | 20 | 1,418 | 55 | Q2 |
| 7 | Journal of Knee Surgery | 13 | 607 | 55 | Q2 |
| 8 | Journal of Pediatric Orthopaedics | 16 | 711 | 49 | Q3 |
| 9 | Orthopaedic Journal of Sports Medicine | 10 | 326 | 49 | Q2/Q3 |
| 10 | Journal of Arthroplasty | 16 | 840 | 47 | Q1 |
| 11 | Clinical Orthopaedics and Related Research | 24 | 2,221 | 43 | Q1 |
| 12 | Sports Medicine and Arthroscopy Review | 16 | 966 | 39 | Q3 |
| 13 | Skeletal Radiology | 14 | 799 | 32 | Q3 |
| 14 | Journal of Bone and Joint Surgery-American Volume | 17 | 1,628 | 29 | Q1 |
| 15 | Orthopaedics & Traumatology-Surgery & Research | 11 | 410 | 29 | Q3 |
| 16 | Journal of Bone and Joint Surgery-British Volume | 17 | 1,405 | 22 | Q1 |
| 17 | Journal of Orthopaedic Research | 14 | 867 | 22 | Q1 |
| 18 | Bone & Joint Journal | 11 | 257 | 16 | Q1 |
| 19 | Clinics in Sports Medicine | 12 | 537 | 14 | Q3 |
| 20 | Journal of Biomechanics | 10 | 366 | 13 | Q3 |

way to identify concepts or topics that were actively discussed during some period of time. **Figure 7B** lists the top 25 references with the strongest citation bursts in chronological order, and the citation strength is represented by the size of the nodes in **Figure 7A**. Reading these papers can help researchers grasp the basis of knowledge more intuitively and quickly.

It can be seen that the most influential reference is Shah JN, 2012 (4), which systematically quantifies the postoperative complications of medial patellofemoral ligament reconstruction in patients with patellofemoral instability - the major complications are patellar fracture, postoperative instability, flexion loss and pain. Among the references with citation burst lasted until 2021, the publication with highest strength was Schneider DK, 2016 (35), which provided a wide range of surgical criteria for isolated medial patellofemoral ligament reconstruction through systematic review and meta-analysis.

Tracking the main research trajectories of a small research field may not be a difficult task, because the scholars don't have to spend a lot of time reviewing a large number of literatures. However, when it is come to study a large research field, it is more difficult and significant for researchers to track the research trajectories. Professor Liu introduced a quantitative method, namely, main path analysis (36), which simplifies large and complex research fields into one or several main trajectories, which are composed of several key nodes and links, as shown in **Figure 7D** (for details of the main research trajectories, see **Supplementary Table S1**).

It can be found that the last node is Steensen R, 2015 (37), which closes all the main trajectories. The significant article analyzed the anatomical factors related to recurrent patellar dislocation through a magnetic resonance imaging study, and put forward the future research direction - the accuracy of risk factor model.

The articles on the main trajectories mainly focus on: (1) epidemiological research and recurrence prediction (38–40), risk factors according to radiography (41–43) of patellar instability; (2) indications (44), surgical techniques (45, 46), clinical prognosis (47–55) and biomechanics research (56, 57) of medial patellofemoral ligament reconstruction;(3) indications and prognosis of osseous operation, such as osteotomy and trochleoplasty (58, 59);(4) the indications for conservative treatment——the difference between prognosis of surgery and conservative treatment (60–62) (5) biomechanical research of knee joint——the posterior stabilizer (63) and the stability of Patellar Alta (64). Besides, it can be found that high-quality RCTs and systemic reviews are more likely to have a significant impact on the research field.

## A Co-Cited Documents-Based Clustering Analysis

A co-cited documents-based clustering analysis can present subfields which represent the main research hotspots (22). **Figure 7C** presents the clusters of the co-citation network of references: "trochleoplasty (cluster #0)," "reconstruction (cluster #1)," "children and adolescents (cluster#2)," "femoral anteversion (cluster#3)," "tibial tuberosity-trochlear groove distance (cluster#4)," "anatomy (cluster#5)," "femoral

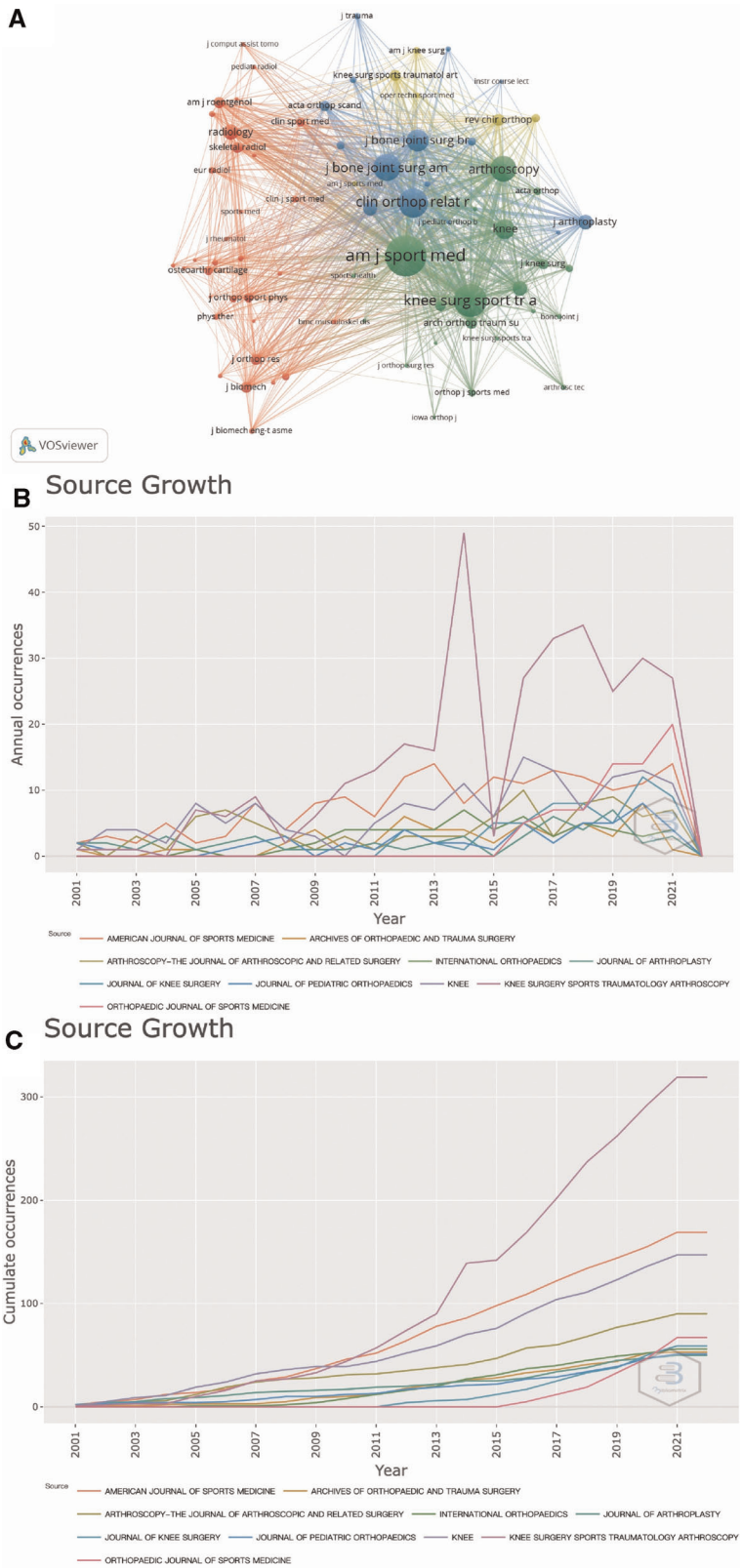


**FIGURE 5** | (**A**) Cluster visualization of the journal co-citation analysis generated by the VOSviewer software. Each node represents a journal, and the size of each circle is determined by the co-citations of the journal. (**B**) Annual publication trend of the prolific journals (**C**) Cumulative publication trend of the top prolific journals.

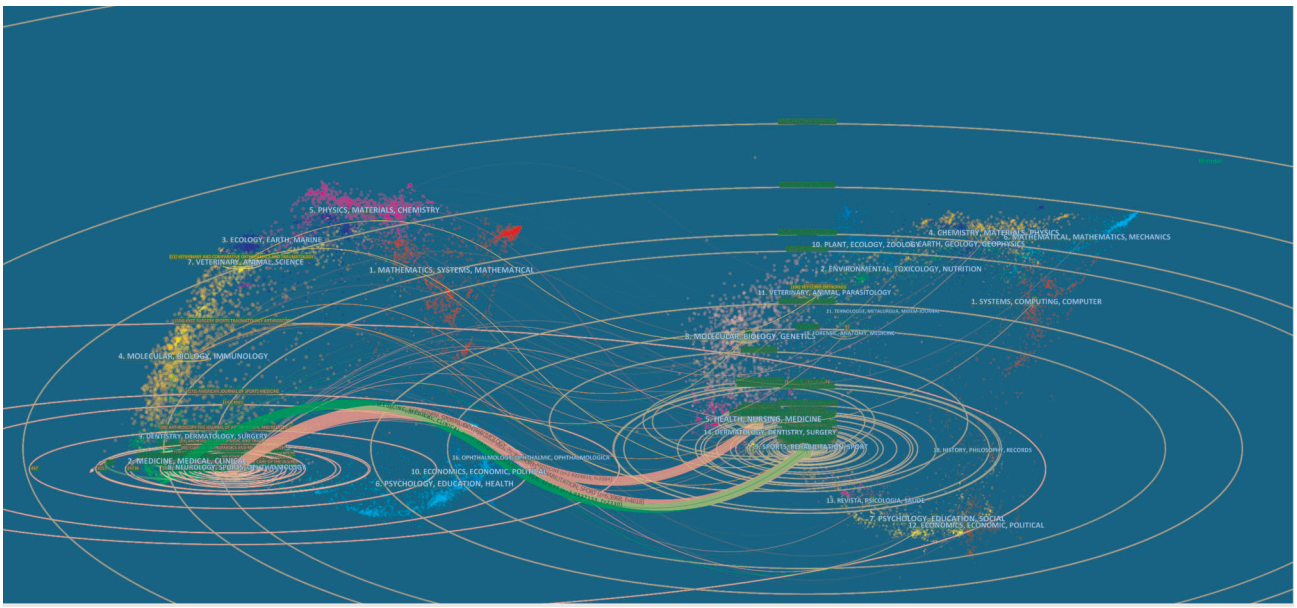


**FIGURE 6** | The dual-map overlay of journals contributed to publications on patellar instability from 2001 to 2021.

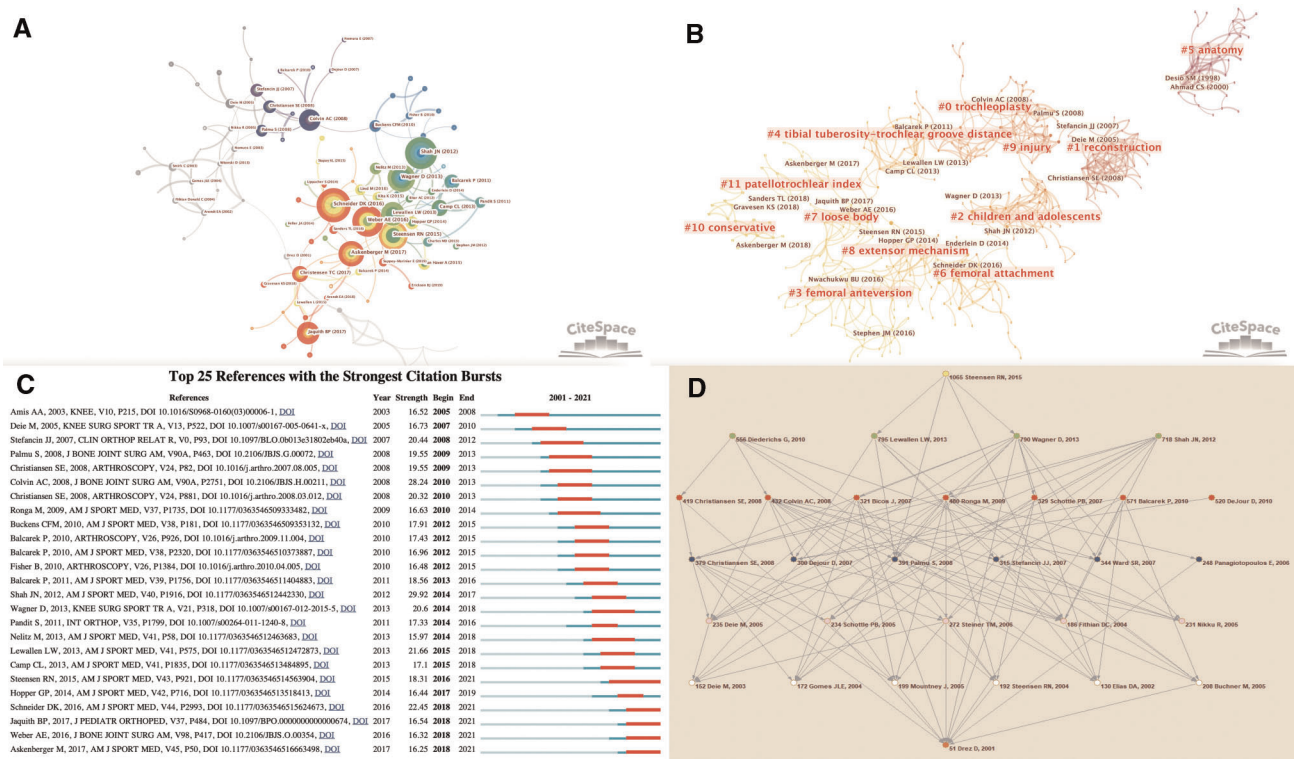


**FIGURE 7** | (**A**) Intellectual base of research on patellar instability. Note: It can be seen that the influential literature has gradually increased in recent years, and more links have been generated. (**B**) The top 25 references with the strongest citation bursts. (**C**) Cluster visualization of the co-citation network of references via Citespace, together with the details and the representative references of the generated clusters. Note: This figure is arranged in chronological order from left to right. (**D**) The research main path during 2001–2021. Note: The research main path analysis is performed based on the algorithm of the Pajek software.

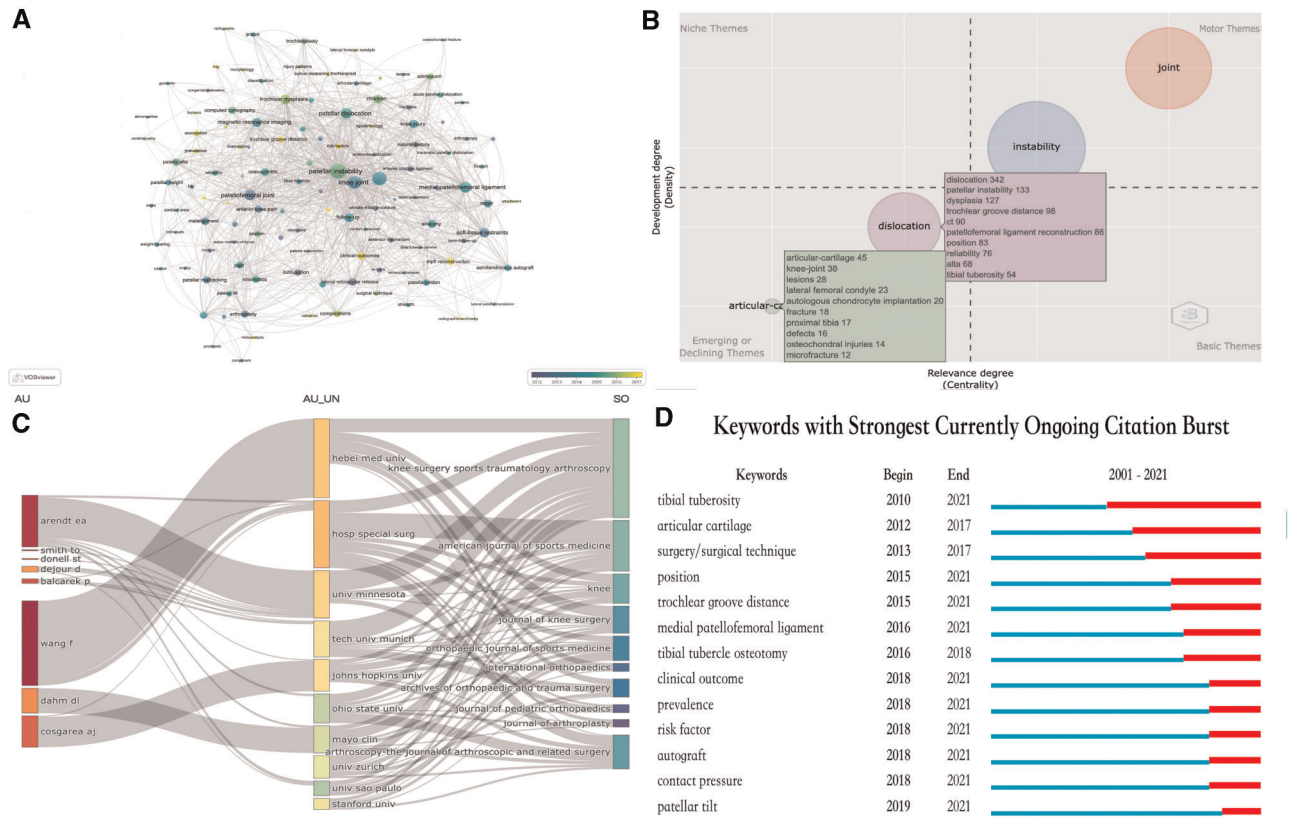


**FIGURE 8** | (**A**) Mapping of keywords based on keywords co-occurrence analysis. (**B**) Thematic map of Keywords generated by the Biblioshiny app. (**C**) The three-field plot showing the knowledge flow. (**D**) Keywords with strongest currently ongoing citation burst.

attachment (cluster#6)," "loose body (cluster#7),""extensor mechanism (cluster#8)," "injury (cluster#9)," "conservative (cluster#10)" and "patellotrochlear index (cluster#11). The cluster setting parameters were as follows: # Years Per Slice = 1, Top *N*% = 5, pruning algorithm was adopted. The Modularity Q score was 0.7123, >0.5 and the Weighted Mean silhouette score was 0.8911 > 0.5, indicating the network was reasonably divided into loosely coupled clusters and the homogeneity within the clusters was credible.

From the change of colors, we can divide the research field into four development stages: Stage I (before 2000): the research mainly focuses on the study of anatomy, which is also the time period during which the French Lyon School made outstanding contributions to the foundation of the research field (65, 66); Stage II (2000–2010): the research mainly focused on trochleoplasty (osseous surgery), medial patellofemoral ligament reconstruction (soft tissue repair) (1, 67, 68); Stage III (2011–2013): the study mainly focused on the indications and complications of surgery in children and adolescents and the application value of TT-TG distance in diagnosis and treatment (69–71); Stage IV (2013–present): the research has gradually deepened, and the research focus has gradually shifted from the femoral attachment and knee extension mechanism(2013–2015) to the treatment of loose body after injury and femoral anteversion (2016–2017), and finally patellotrochlear index and conservative treatment (2018–present) (2, 37, 72).

## Keywords–Co-Occurrence and Research Frontier Analysis

In addition to the reference co-citation analysis, keyword co-occurrence analysis can help us identify the main topics and core contents (73). Therefore, it has become another important research strategy of bibliometrics. Co-occurrence analysis mainly determines the relationship between keywords according to the number of keywords appearing together in a literature. We conducted cleaning and calculation of the data by using VOSviewer software (74), and after setting a selection threshold of 18 for the number of keyword occurrences, we identified 154 relevant keywords. **Figure 8A** shows the overlaying visualization of core keywords in the patellar instability research. The size of nodes reflects the occurrence times of keywords, and the distance between two nodes is directly proportional to the correlation strength between keywords. Besides, all these keywords are also marked with different colors. Relatively early keywords are colored in blue, while recent keywords are colored in yellow.

As is shown in **Figure 8B**, the thematic map generated by R-Bibliometrix software package is displayed in the form of a two-dimensional matrix. The two dimensions of the matrix - centrality and density are represented by the X-axis and Y-axis respectively. The X-axis represents the centrality, that is, the significance of the subject, and the Y-axis represents the density, that is, the centrality of the subject. Accordingly, the upper right quadrant (i.e., quadrant 1) pertains to motor themes that are both important and well-developed, the upper left quadrant (i.e., quadrant 2) is associated with highly developed and isolated themes, the lower left quadrant (i.e., quadrant 3) refers to emerging or declining themes, and the lower right quadrant (i.e., quadrant 4) contains transversal and basic themes. It can be found that there exist two keyword bubbles in the quadrant of emerging or declining themes.

Distinct software based on different algorithms will generate results laying particular emphasis on different aspects, the thematic map generated by the R-Bibliometrix software package, the keyword burst analysis of CiteSpace and the overlapping visualization of VOSviewer are comprehensively utilized (10), so as to accurately identify the frontier in the research field of patellar instability (24). As is shown in **Figure 8**, after overlapping analysis, there are 7 keywords that are identified as potential research frontiers—MPFL (medial patellofemoral ligament) construction, clinical outcome, risk factors, prevalence, articular cartilage, tibial tuberosity and tibial tubercle-trochlear groove (TT-TG) distance. Focusing on making breakthroughs in these research directions will likely yield significant research findings that will greatly give impetus to the field

### MPFL (Medial Patellofemoral Ligament) Construction, Tibial Tuberosity and Tibial Tubercle-Trochlear Groove (TT-TG) Distance

We can find that soft tissue reconstruction (medial patellofemoral ligament construction) and osseous surgery (tibia tubercle anteriomedialis transfer) are still the main research frontiers. Medial patellofemoral ligament construction is one of the most concerned surgical procedures. The gradual deepening of people's understanding of the anatomy and biomechanics of the complex medial patellar retinaculum (75): the proximal medial patellar restraints (MPFL and medial quadriceps tendon-femoral ligament) and the distal medial patellar restraints (medial patellatibial ligament and medial patella meniscal ligament) provides new insight for the medial patellofemoral ligament construction (76). However, the complexity of patellofemoral joint movement and individual differences of patients lead to great disputes among scholars on the selection of attachment point, the tension of reconstructed ligament and MPFL anisometry (77), which are critical factors that influence the overall outcome after MPFL reconstruction.

### Clinical Outcome, Risk Factors and Prevalence

The establishment of multivariate prediction model of patellar instability is difficult but full of potential because of the complex and diverse risk factors of the disease. A variety of variables to consider include: general risk factors such as age, gender, family history, history of congenital dislocation of the hip (78); morphological risk factors included trochlear dysplasia, patellar Alta, a laterally placed tubercle and patellar tilt (79); In addition, the results of physical examination and imaging risk factors need to be included. These variables are important perioperative indicators that do not involve surgical technology. The establishment of multivariable model and the application of radiomics can provide long-term and reliable medical management for patients (80), so as to prevents morbidity in high-risk patients and improve the prognosis of patients to a certain extent. However, due to the lack of the number of clinical cases and long-term and reliable clinical research results, the establishment of the model is still difficult, but some breakthroughs have been made. For example, Duerr, Robert A established an algorithm model to manage recurrent patellar dislocation (81).

In the choice between conservative management and surgical treatment, including MPFL reconstruction, trochleoplasty, tibial tubercle transfer and femoral rotational osteotomy, we need to comprehensively consider the complications of the treatments, the probability of recurrence and the performance of patients returning to exercise. Therefore, the clinical outcomes of treatment have been the research focus of researchers for a long time, and therefore can produce more influential articles in the future.

### Articular Cartilage

Patellofemoral joint can cause cartilage injury in the early stage, leading to the development of osteoarthritis. Most surgical operations only focus on the treatment of patellar instability, do not treat the damaged cartilage, and there is a lack of corresponding high-level clinical research (82). The treatment of cartilage is a very dynamic research frontier. In addition to conventional arthroscopic chondral debridement, the rapid development of technologies and biomaterials makes this field full of possibilities, including autologous matrix-induced chondrogenesis (AMIC) combining microfracture with collagen I / III matrix (83), autologous osteochondral transplantation or inlay, and the introduction of matrix-assisted autologous chondrocyte transplantation (MACT) procedure in the first-generation of autologous chondrocyte implantation (ACI) (84), and cartilage regeneration technology of osteochondral scaffolds (85). It can be expected that in the future, with the in-depth understanding of the etiology and biomechanics of cartilage degenerative diseases, more advanced and effective treatments will appear, so as to obtain great influence.

## LIMITATIONS

There are still some limitations in our current research.

Firstly, there are certain limitations in our study. Firstly, in our study, we only searched the Web of Science Core Collection (WoSCC) and did not incorporate other databases,

such as PubMed, Scopus or Embase. However, it may be unscientific to merge and analyze the data from multiple databases, because different databases have different measurement of citation frequency counting and classification of publications (9, 86).

Secondly, only English publications were included, which may lead to the omission of a portion of high-quality articles published in other languages.

Finally, there existed two potential disadvantages: (1) there was no manual cleaning of the sample data before formal analysis; (2) because the analyses were completed by software, there might be some errors or biases in our results. For example, the name of the journals may be changed over a long period of time. In addition, two authors with the same name may be repeatedly accumulated.

## CONCLUSIONS

This is the first comprehensive bibliometric analysis of patellar instability. Our results show that patellar instability has gradually attracted the attention of scholars, which can be seen from the increasing number of articles and citations year by year. So far, the United States has been in a leading position in this field. Hospital for special surgery and Andrew A Amis are the most prolific institutions and the most influential authors respectively. The American Journal of Sports Medicine and Knee Surgery Sports Traumatology Arthroscopy are the most influential and productive journals in the study of patellar instability, with the most citations and publications respectively. According to the analysis of references, we identified 11 research hotspots of patellar instability in chronological order, and identified the main research paths in this field. In addition, the comprehensive analysis of keywords identified mpfl (medial patellofemoral ligament) construction, clinical outcome, risk factors, prevalence, articular cartilage, tibial tuberosity and tibial tubercle-trochlear groove (TT-TG) distance as significant research directions in the future, which deserves the attention of researchers. In short, scholars, especially researchers newly entering this industry, can benefit from our research, which can enable them to clearly and quickly understand the global hotspots, trends and knowledge structure of this field, so that they can be inspired to a certain extent.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

## AUTHOR CONTRIBUTIONS

QW: project administration, validation data curation and supervision. ZZ: conceptualization, methodology, data curation, formal analysis, and writing—original draft. WX: methodology, writing—review, and editing. All authors contributed to the article and approved the submitted version.

## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/article/10.3389/fsurg.2022.870781/full#supplementary-material.

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# Prevalence and Risk Factors of Surgical Treatment for Klippel–Feil Syndrome

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**Background:** Recently, there have been some reports on surgical treatment for Klippel–Feil syndrome, but the prevalence and risk factors of surgery have not been well evaluated. This study sought to find the prevalence and potential risk factors of surgical treatment.

**Methods:** A retrospective radiographic review of 718 Klippel–Feil syndrome patients seen at Peking University Third Hospital from January 2010 to October 2017 was performed. Parameters included age, gender, deformity, cervical instability, Samartzis classification, and surgical treatment. Based on the surgical treatment they received, patients were divided into a surgery group and a non-surgery group. Prevalence and possible risk factors of surgical treatment were assessed.

**Results:** A total of 718 Klippel–Feil syndrome patients, including 327 men and 391 women, with an average age of 46.8 years were enrolled. According to the Samartzis classification scheme, 621 cases (86.5%) were classified as type I, 48 cases (6.7%) were classified as type II, and 49 cases (6.8%) were classified as type III, respectively. The most commonly fused segments were C2–3 (54.9%) and C5–6 (9.3%). Of all 718 patients, 133 (18.5%) patients underwent surgical treatment, mainly via the posterior approach (69.9%). The clinical factors included age, gender, deformity, instability, and Samartzis classification. Men were more likely to require surgical treatment ($p < 0.001$). Patients with instability ($p < 0.001$) or patients with deformity ($p = 0.004$) were also more likely to undergo surgery. All three of these variables were included in the binary regression analysis. Finally, gender ($p < 0.001$) and unstable joints ($p < 0.001$) were identified to be independently associated with surgical treatment. Gender was the most important risk factor with men being 2.39 times more likely to have surgical treatment, while patients with instability were 2.31 times more likely to receive surgery.

**Conclusion:** The prevalence of patients with Klippel–Feil syndrome requiring surgery was 18.5%, with the majority undergoing posterior cervical surgery. Gender and instability were indemnified as independent risk factors leading to surgical treatment.

**Keywords: Klippel–Feil syndrome, surgical treatment, prevalence, risk factors, Samartzis classification**

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## INTRODUCTION

Klippel–Feil syndrome (KFS) is a rare congenital cervical fusion condition, first described by Maurice Klippel and Andre Feil in 1912 (1). It is characterized by the congenital fusion of ≥2 cervical vertebrae, resulting from abnormal embryonic development during the first 3–8 weeks of gestation (2). The typical clinical triad of a low posterior hairline, a short neck, and restricted neck motion was originally recognized as the hallmark of KFS (3, 4), but numerous spinal and extraspinal anomalies have now been documented in KFS patients (5–8).

The global incidence of KFS is estimated to be 0.71% (9, 10), and the condition mainly affects female individuals (60% cases). However, the exact prevalence of this condition has not been well assessed due to the fact that asymptomatic patients without an obvious physical deformity are often not found to have KFS until a clinical event such as trauma requires cervical spine imaging (3, 11, 12). Therefore, the usage of radiology remains an important way to detect and evaluate KFS.

The fusion patterns of KFS patients are widely classified as single fusion, multi-continuous fusion, and multi-non-continuous fusion, as defined in the Samartzis classification (13). Patients with persistent myelopathy or radiculopathy, instability, or deformity warrant consideration for surgical treatment (14, 15). Our aim was to identify the factors leading to surgery for KFS patients and to validate the prevalence of KFS based on the Samartzis classification.

## MATERIALS AND METHODS

### Subjects and Data

This study was a retrospective radiographic review of KFS patients at Peking University Third Hospital, Beijing, China. After receiving Institutional Review Board approval from Peking University Third Hospital (IRB no:160-02), we searched our radiographic system using the key term "cervical fused segments" and found 1,014 patients with cervical fused segments, 296 of whom were subsequently excluded. Of these excluded patients, 86 patients did not have congenitally fused cervical segments, 181 patients only had an occipital fusion, and 12 patients only had a fusion between C7 and thoracic vertebra, while 17 patients lacked demographic information. We finally enrolled 718 consecutive KFS patients with basic information and complete radiographic records seen from January 2010 to October 2017 for the analysis.

### Parameters and Variables

Radiographs collected during the evaluation of KFS patients entailed cervical lateral, anteroposterior (AP), extension, and flexion views along with computed tomography (CT) scanning as well as magnetic resonance imaging (MRI) of the cervical spine. Radiographs were initially used to verify diagnoses and then reviewed to identify congenitally fused segments, which were defined as congenital bone bridges between the adjoining vertebrae or posterior elements without movement during flexion and extension. Each patient's age and gender were obtained, and their clinical history with presenting symptoms and the use of surgical or non-surgical treatment were analyzed. When surgical treatment was performed, the approach of the surgery was noted and collected. All radiographic evaluations were performed by an orthopedic spine surgeon, and crucial radiographic parameters consisting of the number of congenitally fused segments (C1–7), whether the patient had a single fusion or multiple fusions, and the presence of atlantooccipital fusion were also evaluated. Each radiograph was classified using the Samartzis classification scheme (**Figure 1**).

The instability of cervical segments was evaluated according to previously defined metrics. Patients with neck pain, headache, or neurological signs should be screened for cervical spine instability. Atlantoaxial instability (AAI) was defined as an anterior atlantodental interval (ADI) of >3 mm. Subaxial translation in the C3–7 vertebrae (SAS) was defined as a 2-mm translation of horizontal displacement of a single vertebra in relation to an adjacent vertebra. Additionally, the following types of deformity were considered: musculoskeletal deformity (defects of cervical vertebral formation, defects of thoracic vertebrae, and abnormalities in alignment), neural deformity (basilar invagination and Chiari malformation), and other deformities (torticollis). Moreover, information about whether the patient received surgical treatment was collected, and the surgical approach (e.g., anterior, posterior, or both) was recorded. The indications of surgery were radiculopathy or myelopathy symptoms, spinal cord compression, and instability of the cervical spine (mainly AAI). Surgery type and approach were decided upon by individual surgeons.

### Statistical Analysis

Statistical analysis was performed using SPSS version 26.0 (IBM Corporation, Armonk, NY, USA). Initial descriptive and frequency statistics were conducted. A chi-squared analysis of categorical variance was conducted, and Fisher's exact test was considered when the cell count was less than 5. An appropriate *t*-test, correlation test analysis, parametricity analysis, and logistic regression modeling were performed. All statistical testing was two-sided. Statistical significance was established as $p < 0.05$.

## RESULTS

### Population

A total of 718 KFS patients, including 327 men (45.5%) and 391 women (54.5%), were enrolled in this study. The mean age of the study participants was 46.8 years old (range, 4–92 years; standard deviation, 16.986 years). The most common level of congenitally fused segments was C2–3 (54.9%, 134 cases were C2–3 with atlantooccipital fusion) followed by C5–6 (9.2%) and C3–4 (8.5%). Additional frequencies of fusion levels are demonstrated in **Table 1**. With regards to the Samartzis classification, 621 patients (86.5%) were classified as type I, 48 patients (6.7%) were classified as type II, and 49 patients

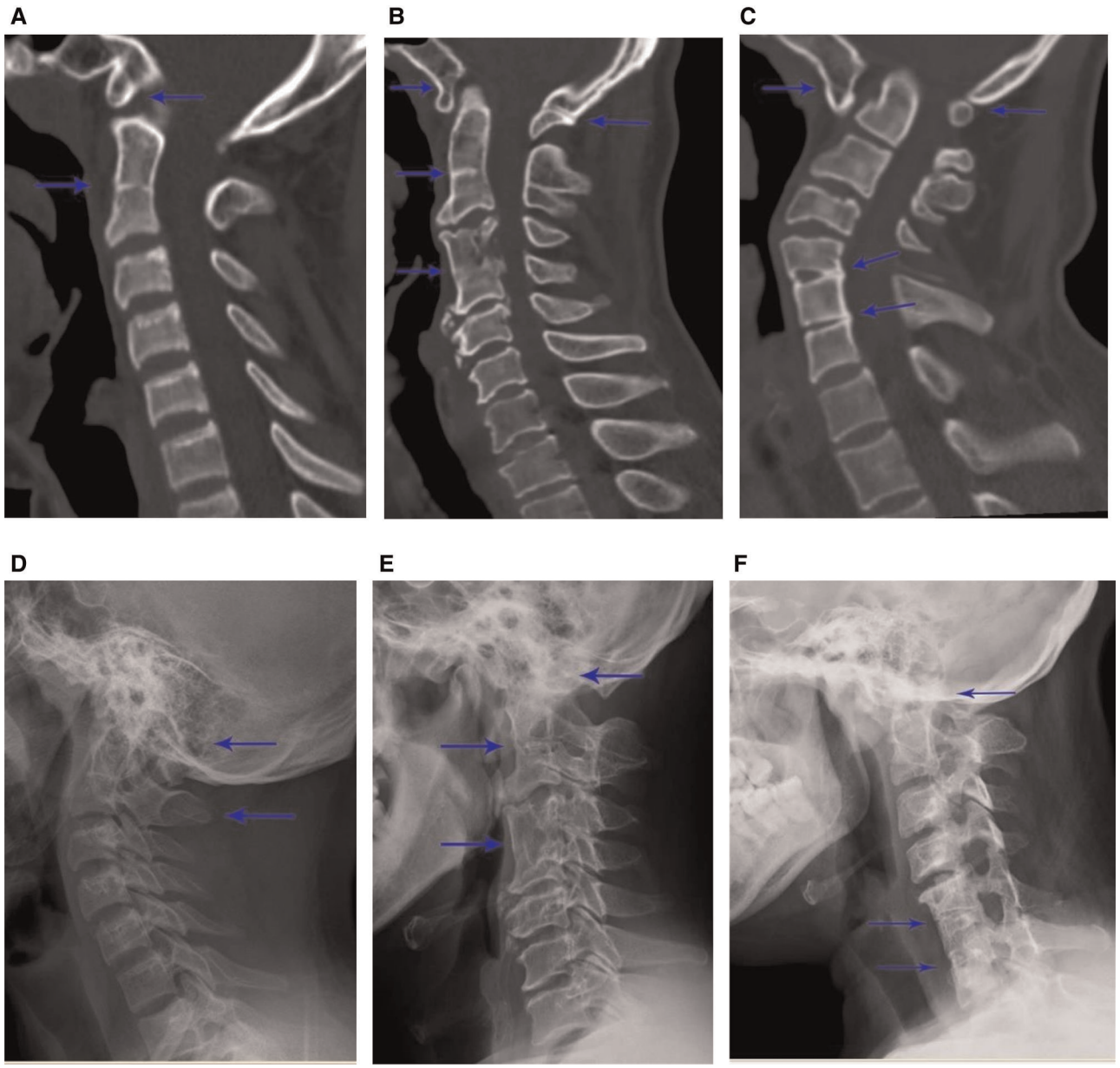


**FIGURE 1** | Patients with Klippel–Feil syndrome (KFS) and occipital fusion. Examples of different types of KFS patients with occipital fusion: type I – (**A**) computed tomography (CT) scan and (**D**) radiograph showing C2–3 single fusion with occipital fusion; type II – (**B**) CT scan and (**E**) radiograph showing noncontiguous levels of fusion (C2–3 and C4–5) with occipital fusion; type III – (**C**) CT scan and (**F**) radiograph showing three levels of contiguous fusion at C5-7 with occipital fusion. The site of fusions is indicated by *arrows*.

(6.8%) were classified as type III cases. Stratification of the classification type by gender was also performed (**Table 2**).

## Surgical Treatment

Of the 718 enrolled KFS patients, 133 (18.5%) received surgical treatment, including 82 men (61.7%) and 51 women (38.3%). In total, 17.7% type I patients, 27.1% type II patients, and 20.4% type III patients were treated with surgery. Percentages of fusion levels managed with surgical treatment are shown in **Table 3**.

We also recorded the surgical approach (e.g., anterior, posterior, or both) of KFS patients who had undergone surgical treatment. The results showed that 33 patients (24.8%) received the anterior approach, 93 patients (69.9%) were treated through the posterior approach, and 7 patients (5.3%) underwent surgery using both approaches (**Table 4**). The distribution of various indications for surgical approaches is shown in **Table 5**

**TABLE 1** | Distribution of congenital fusion levels.

| Samartzis classification | Congenital fusion level | Frequency (%) |
|---|---|---|
| Type I | O–C1 with C1–2 | 2 (0.3%) |
| | C1–2 | 2 (0.3%) |
| | O–C1 with C2–3 | 134 (18.7%) |
| | C2–3 | 260 (36.2%) |
| | O–C1 with C3–4 | 1 (0.1%) |
| | C3–4 | 60 (8.4%) |
| | O–C1 with C4–5 | 2 (0.3%) |
| | C4–5 | 57 (7.9%) |
| | C5–6 | 67 (9.3%) |
| | O–C1 with C6–7 | 1 (0.1%) |
| | C6–7 | 35 (4.9%) |
| Type II | O–C1 with multi | 14 (1.9%) |
| | Multi | 34 (4.7%) |
| Type III | O–C1 with multi | 3 (0.4%) |
| | Multi | 46 (6.4%) |

**TABLE 2** | The incidence of Klippel–Feil syndrome (KFS) classification types to gender.

| Samartzis classification | Male | Female |
|---|---|---|
| Type I | 283 (45.6%) | 338 (54.4%) |
| Type II | 22 (45.8%) | 26 (54.2%) |
| Type III | 22 (44.9%) | 27 (55.1%) |

**TABLE 3** | The distribution of surgical treatment in fusion levels.

| Samartzis classification | Congenital fusion level | Surgery (Total) | Percentage |
|---|---|---|---|
| Type I | C1–2 with O–C1 | 1 (2) | 50% |
| | C1–2 | 1 (2) | 50% |
| | C2–3 with O–C1 | 28 (134) | 20.9% |
| | C2–3 | 29 (260) | 11.1% |
| | C3–4 with O–C1 | 0 (1) | 0 |
| | C3–4 | 14 (60) | 23.3% |
| | C4–5 with O–C1 | 0 (2) | 0 |
| | C4–5 | 13 (57) | 22.8% |
| | C5–6 | 17 (66) | 25.8% |
| | C6–7 with O–C1 | 1 (1) | 100% |
| | C6–7 | 6 (35) | 17.1% |
| Type II | Multi with O–C1 | 7 (14) | 50% |
| | Multi | 6 (34) | 17.6% |
| Type III | Multi with O–C1 | 1 (3) | 33.3% |
| | Multi | 9 (46) | 19.6% |

**TABLE 4** | The distribution of the type of surgery.

| Samartzis classification | Type of surgery | | |
|---|---|---|---|
| | Anterior | Posterior | Both |
| Type I | 29 (26.4%) | 78 (70.9%) | 3 (2.7%) |
| Type II | 2 (15.4%) | 9 (69.2%) | 2 (15.4%) |
| Type III | 2 (20.0%) | 6 (60.0%) | 2 (20.0%) |

**TABLE 5** | The distribution of various indications for surgery approaches.

| Indication | Type of surgery | | |
|---|---|---|---|
| | Anterior | Posterior | Both |
| Deformity | | | |
| Yes | 6 (14.6%) | 30 (73.2%) | 5 (12.2%) |
| No | 27 (29.3%) | 63 (68.5%) | 2 (2.2%) |
| Instability | | | |
| Yes | 8 (17.8%) | 34 (75.6%) | 3 (6.7%) |
| No | 25 (28.4%) | 59 (67.0%) | 4 (4.5%) |

**TABLE 6** | Comparison of patients with or without surgical treatment.

| Variable | Surgery ($n = 133$) | Non-surgery ($n = 585$) | $p$-value |
|---|---|---|---|
| Mean age (year) | 47.24 ± 17.65 | 46.70 ± 16.85 | 0.741[a] |
| Age (year) | | | 0.716[b] |
| <60 | 105 (78.9%) | 470 (80.3%) | |
| ≥60 | 28 (21.1%) | 115 (19.7%) | |
| Gender | | | <0.001[b] |
| Male | 82 (61.7%) | 245 (41.9%) | |
| Female | 51 (38.3%) | 340 (58.1%) | |
| Deformity | | | 0.004[b] |
| Yes | 41 (30.8%) | 113 (19.3%) | |
| No | 92 (69.2%) | 472 (80.7%) | |
| Instability | | | <0.001[b] |
| Yes | 45 (33.8%) | 100 (17.1%) | |
| No | 88 (66.2%) | 485 (82.9%) | |
| Samartzis classification | | | 0.257[b] |
| Type I | 110 (82.7%) | 511 (87.4%) | |
| Type II | 13 (9.8%) | 35 (6.0%) | |
| Type III | 10 (7.5%) | 39 (6.7%) | |

[a]*p-value by t-test.*
[b]*p-value by* $\chi^2$.

## Risk Factors

In all, 133 of the 718 KFS patients underwent surgical treatment. The clinical factors we acquired included age, gender, deformity, instability, and Samartzis classification. The comparisons and evaluation of parameters are summarized in **Table 6**. Male patients ($p < 0.001$), instability ($p < 0.001$), and deformity ($p = 0.004$) were factors that increased the chance of receiving surgery.

All three variables (gender, instability, and deformity) were included in the binary logistic regression analysis (**Table 7**). Gender ($p < 0.001$) and unstable joint ($p < 0.001$) were finally identified to be independently associated with surgical treatment. Gender was the most crucial risk factor with men being 2.39 times more likely to undergo surgical treatment, while KFS patients with instability were 2.31 times more likely

**TABLE 7** | Result of logistic regression.

| Variable | OR | 95% CI | *p*-value |
|---|---|---|---|
| Gender (male) | 2.392 | 1.611, 3.522 | <0.001 |
| Deformity (yes) | 1.470 | 0.920, 2.348 | 0.107 |
| Instability (yes) | 2.312 | 1.458, 3.668 | <0.001 |

*Abbreviations: OR, odds ratio; CI, confidence interval.*

to undergo surgery. The deformity was not confirmed as a potential independent risk factor for surgical treatment.

## DISCUSSION

KFS is a rare disease, characterized as a condition of congenital fusion of at least two cervical vertebrae. The diagnosis of KFS is usually made based on clinical features and radiographic evaluations including plain radiographs (X-rays), CT, and MRI. However, the clinical triad of KFS is found in less than 50% KFS patients, and recent studies have shown that most sporadic KFS cases are identified by the radiographic evaluation performed incidentally as a lot of cases have asymptomatic single fused cervical segments (11, 16).

In this study, all radiographs of KFS patients treated at Peking University Third Hospital between January 2010 and October 2017 were evaluated. Of the 718 KFS patients that met the study inclusion criteria, 45.5% cases involved male patients, and 54.5% involved female patients. The most common levels of congenitally fused segments were C2–3 (54.9%) and C5–6 (9.2%), coinciding with the findings of previous literature. Further, there were 621 type I, 48 type II, and 49 type III cases, and it was clear that type I (86.5%) was the most common Samartzis classification in our study.

Regarding the surgical treatment, we found that 133 of the 718 (18.5%) enrolled KFS patients were treated by surgery, including 82 men (61.7%) and 51 women (38.3%). Of them, 33 patients (24.8%) took the anterior approach, 93 patients (69.9%) received surgery via the posterior approach, and 7 patients (5.3%) were treated using both approaches.

We evaluated the parameters to find possible risk factors. It seemed that gender, instability, and deformity were associated with KFS surgical treatment. Following the binary logistic regression analysis, gender and instability were identified as independent risk factors. Gender was the most crucial risk factor with men being 2.39 times more likely to undergo surgical treatment, while KFS patients with instability were 2.31 times more likely to receive surgery. However, we could not find any clear direct relationship between gender and surgery, so more studies are needed to demonstrate this.

The surgical treatment of patients with KFS presenting with radiculopathy or myelopathy manifestations, deformity, or definite instability is necessary (14, 15). In this context, anterior surgical treatment includes anterior cervical discectomy and fusion and anterior cervical corpectomy and fusion (17), while posterior surgery mainly consists of decompression and fusion surgical treatment (18). Emergency fusion surgery should be considered when the patients present with an unstable cervical spine, such as with the presence of foramen magnum occipitalis stenosis, basal ganglia depression, or any radiological evidence of progressive cervical instability.

Our study validated the previous study by Samartzis et al. (13), who reported an increased frequency of KFS in women (**Table 2**). However, we found that surgical treatment did not appear to be more prevalent in any single type of KFS. Our study demonstrated that up to 75.6% patients may undergo posterior fusion with laminectomy to address instability and myelopathy.

There were 145 patients (20.2%) diagnosed with instability in our report, and 31% of them underwent the surgery. The report from Samartzis et al. (19) demonstrated that a thorough evaluation given a high risk of cervical instability (cranial subluxation or atlantoaxial rotational subluxation) is necessary for patients with KFS. In their study, KFS patients were treated with surgery according to their instability status. This is consistent with our finding that instability is a potential independent risk factor for surgical treatment.

Nouri et al. (20) conducted a study that included the imaging data and clinical characteristics of 592 patients, including 14 diagnosed with KFS. They found that the center of the cervical spine was closely associated with spinal cord compression; spinal cord compression was found below the level of C3/4 fusion and above (9/10), while the compression was found above the plane of C5/6 fusion and below (8/8). As for the fusion level of C4/5, spinal cord compression was found in adjacent segments above and below. Surgery for myelopathy seemed to occur at center levels of the cervical spine, but the Samartzis classification, which categorizes different fusion levels of cervical segments, was found to have nothing to do with the decision to proceed to surgical treatment ($p = 0.257$).

Regarding spinal deformity, 154 patients in our study had a deformity, and 26.6% of them finally underwent surgery. Zhou et al. (21) suggested that patients with KFS tend to have spinal deformities and non-neurological deformities, and more KFS patients chose to undergo decompression surgery than not in their study. Hachem et al. (22) defined KFS patient phenotypes that were associated with surgical intervention through the principal component analysis and proposed that cervical spine surgery was associated with axial cervical spine anomalies and cervical subluxation, while cranial surgery had a high association with Chiari malformation. We were unable to find a specific relationship of deformity in the absence of Chiari malformation that showed an increased requirement for surgical intervention.

Limitations to our study include its retrospective nature, whereby patients who already showed symptoms were referred to our institution leading to a greater prevalence of surgical intervention in this study. The choice for surgery was also made by several surgeons, thereby leading to the heterogeneity of surgical treatment. Although we enrolled a large sample of patients who were diagnosed with KFS, most cases involved C2–3 fusion, which would make it hard to identify the

correlation between risk factors and KFS prevalence. Further studies are warranted to find the exact risk factors of KFS surgical treatment and to test the exact correlation between deformity and KFS surgical treatment.

## CONCLUSION

We present a large analysis of KFS patients and their receipt of surgical treatment. In our study, the most prevalent pattern was Samartzis type I, defined as a single congenitally fused cervical segment, and the most common level of congenitally fused segments was C2–3. With regards to surgical treatments, the prevalence was 18.5%, and most operations were conducted via the posterior approach. However, gender and instability were identified as independent risk factors associated with surgical treatment. Gender was the most crucial risk factor with men being 2.39 times more likely to undergo surgical treatment than women, and KFS patients with instability were 2.31 times more likely to receive surgery. However, the deformity was not proven to be a potential independent risk factor for surgical treatment.

## DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Boards of Peking University Third Hospital. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

## AUTHOR CONTRIBUTIONS

LD: design, collection of data, manuscript, editing, approval of final version, and accountability. XM and FfZ: design, collection of data, editing, and approval of the final version. LD, XW, YS, FsZ, SP, XC, YD, YZ, TX, WL, and FfZ revised the manuscript for important intellectual content. All authors contributed to the article and approved the submitted version.

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# Vancomycin Containing PDLLA and PLGA/β-TCP Inhibit Biofilm Formation but Do Not Stimulate Osteogenic Transformation of Human Mesenchymal Stem Cells

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**Aims:** Chronic osteomyelitis, including implant-related prosthetic joint infection, is extremely difficult to cure. We develop vancomycin containing release systems from poly(D,L-lactide) (PDLLA) and poly(D,L-lactide-co-glycolide) (PLGA) composites with beta-tricalcium phosphate (β-TCP) to treat methicillin-resistant *Staphylococcus aureus* osteomyelitis. We ask whether vancomycin containing PDLLA/β-TCP and PLGA/β-TCP composites will prevent early biofilm formation, allow cell proliferation and osteogenic differentiation, and stimulate osteogenic signaling molecules in the absence of an osteogenic medium.

**Methods:** Composites were produced and characterized with scanning electron microscopy. *In vitro* vancomycin release was assessed for 6 weeks. Biofilm prevention was calculated by crystal violet staining. Human bone marrow-derived mesenchymal stem cells (hBM-MSCs) and osteosarcoma cell (SaOS-2) proliferation and differentiation were assessed with water soluble tetrazolium salt and alkaline phosphatase (ALP) staining. Real-time quantitative polymerase chain reaction defined osteogenic signaling molecules for hBM-MSCs.

**Results:** Totally, 3.1 ± 0.2 mg and 3.4 ± 0.4 mg vancomycin released from PDLLA/β-TCP and the PLGA/β-TCP composites, respectively, and inhibited early biofilm formation. hBM-MSCs and SaOS-2 cells proliferated on the composites and stimulated ALP activity of cells. Runt-related transcription factor 2 (RUNX2) and SRY-Box transcription Factor 9 (SOX9) expressions were, however, lower with composites when compared with control.

**Conclusion:** Vancomycin containing PDLLA/β-TCP and PLGA/β-TCP composites inhibited early biofilm formation and proliferated and differentiated hBM-MSCs and SaOS-2 cells, but osteogenesis-related RUNX2 and SOX9 transcription factors were not strongly expressed in the absence of an osteogenic medium for 14 days.

**Keywords: vancomycin, PDLLA, PLGA, β-TCP, biofilm, bone signaling molecules**

## INTRODUCTION

Chronic osteomyelitis is a bone infection leading to tissue damage and destruction with severe local and systemic morbidity (1) and mortality (2). The incidence of periprosthetic joint infection (PJI), which is a specific type of osteomyelitis, is mostly recognized by biofilm formation on an implant by methicillin-resistant *Staphylococcus aureus* (MRSA) that is between 0.3% and 3.0%, and mortality may increase up to 18% at revision (3). Average hospitalization costs in the US can be between 25.000 and 32.000 USD (4), which necessitates the development of new treatment strategies for the prevention and treatment of PJI.

Combining antibiotics with poly-methylmethacrylate (PMMA) is the standard treatment for PJI (5); however, PMMA has several drawbacks such as being a nonbiodegradable polymer and triggering the necessity for a second surgery for its removal. As PMMA shows an exothermic reaction during polymerization, only heat-stable antibiotics can be used with this polymer (6). Degradable composites are, therefore, used these days (7) to minimize the disadvantages of the non-degrading biomaterials. These composites should be active against the pathogens involved in the infection, release antibiotics at least 10 times higher than the minimum inhibitory concentration, should be biocompatible, and stimulate bone formation (8). Poly(D,L-lactide) (PDLLA) and poly(D,L-lactide-co-glycolide) (PLGA) are biodegradable and biocompatible polymers generally used as carriers in drug delivery systems (9). The disadvantages of these polymers are their acidic products after the biodegradation. The acidic products decrease the pH of the environment and fasten further degradation. Also, these polymers have low cell adhesion potential (10). On the other hand, beta-tricalcium phosphate (β-TCP) is a biodegradable bioceramic used in local drug delivery systems due to its high solubility rate and faster degradation time (11, 12). It also shows osteointegration and osteoconduction properties (13).We previously studied (14, 15) vancomycin containing PDLLA/β-TCP on human bone marrow-derived mesenchymal stem cells (hBM-MSCs) and osteosarcoma cell (SaOS-2) *in vitro* and on rats with experimental implant-related osteomyelitis *in vivo* for its drug release capability and biocompatibility; however, we did not assess its osteogenic potential. PLGA (16, 17) was evaluated for its vancomycin release and delivery capacity against infection. PLGA was also assessed for its osteogenic potential in a study by Yoon et al. (18). β-TCP was studied as a drug carrier (19), and a study (20) focused on the osteogenic potential of the material previously. We hypothesized that vancomycin containing PDLLA/β-TCP and PLGA/β-TCP composites will stimulate osteogenesis due to its high β-TCP content. Our research questions were whether vancomycin containing PDLLA/β-TCP and PLGA/β-TCP composites may prevent early biofilm formation, allow cell proliferation and osteogenic mineralization, and stimulate osteogenic signaling molecule expression of hBM-MSCs in the absence of the osteogenic medium.

We aimed for the evaluation of vancomycin release from PDLLA/β-TCP and PLGA/β-TCP composites to prevent early MRSA biofilm inhibition. Cytocompatibility and mineralization capacity of these composites were further assessed by water soluble tetrazolium salt (WST) and alkaline phosphatase (ALP) staining. Osteogenic signaling molecule expression of hBM-MSCs cultured with composites were evaluated using real-time quantitative polymerase chain reaction (qRT-PCR).

## MATERIALS AND METHODS

### Design

A controlled *in vitro* study was designed. Independent variables were groups and time, while dependent variables were vancomycin release, antibiotic susceptibility, early biofilm inhibition, cell proliferation, ALP activity, and osteogenic potential of the composites with qRT-PCR. The design of the composites is given in **Figure 1**.

### Materials

PLGA and PDLLA were purchased from Evonik Industries (Essen, Germany) and vancomycin hydrochloride was purchased from Zhejiang Medicine Co. Ltd. (Zhejiang, China). β-TCP was purchased from BMT Calsis (Ankara, Turkey). Dichloromethane (JT Baker, PA, USA) was used to dissolve the polymers. In order to prepare vancomycin containing PLGA/β-TCP composites, a total of 8,574 mg of PLGA was dissolved in 40 ml of dichloromethane. Then, 5,355 mg of vancomycin hydrochloride powder was added into the solution, followed by the addition of 16,071 mg β-TCP. The mixture was stirred on a magnetic stirrer with a closed lid and dried at room temperature for 24 h. After the evaporation of dichloromethane, the remaining powdery structure was ground on a porcelain mortar. For vancomycin containing PDLLA/β-TCP composites, all procedures mentioned above were repeated, but this time, 8,574 mg of PDLLA was used instead of PLGA. The powders were hand-pressed in a tablet-pressing machine, and totally, 149 vancomycin containing PLGA/β-TCP composite discs and 160 vancomycin containing

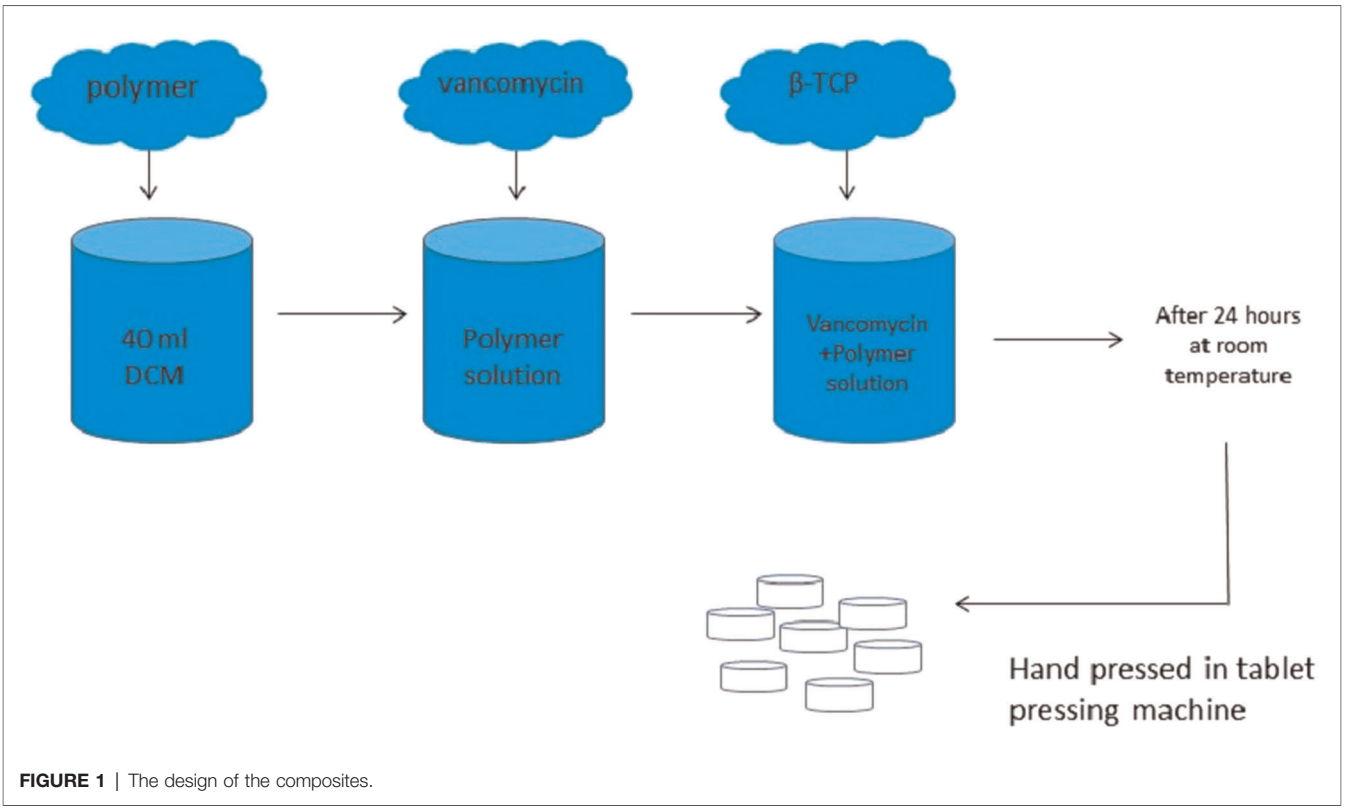


**FIGURE 1** | The design of the composites.

PDLLA/β-TCP composite discs were obtained. The composite discs had a 3 mm height with 6 mm diameter. The final content ratios of the composites were 53.6% β-TCP, 28.6% polymer, and 17.8% vancomycin hydrochloride.

## Characterization of Composites

Surface topography and composition of the composites were characterized by using a scanning electron microscope (SEM; Nova Nanosem 430, Fei, OR, USA) with a built-in X-ray energy-dispersive spectrometer (EDS). The composites were fixed on supports and coated with gold film to obtain a conducting surface before the analysis.

The vancomycin containing composite discs were further evaluated by using a Fourier transform infrared microscope, which attenuated total reflection (FTIR-ATR; Bruker Alpha, Bruker, MA, USA). PLGA, PDLLA, β-TCP, and vancomycin were also analyzed to determine the similarities and differences between the composite discs and plain materials. The infrared spectrum was collected in the range of 4,000–400 $cm^{-1}$ with a resolution of 4 $cm^{-1}$ and a scan number of 24.

## *In Vitro* Vancomycin Release

Vancomycin containing composite discs from each group ($n$ = 6) were immersed into a 50 ml phosphate buffered saline (PBS) containing polystyrene tubes. PBS was prepared by dissolving one PBS tablet (Oxoid, Hampshire, UK) in 100 ml distilled water. The tubes were placed into a hot water bath at 37°C and shaken constantly at 30 rpm. At predetermined time points (1, 2, 4, 8, 12, 24, 48, and 120 h and 1, 2, 3, 4, 5, and 6 weeks), 1 ml PBS was withdrawn and replaced with an equal amount of fresh PBS. The withdrawn solutions were analyzed spectrophotometrically with a Nanodrop ND 1000 spectrophotometer (Thermo Scientific, MA, USA) at 280 nm with a 1:10 dilution factor. A calibration curve for vancomycin was generated to calculate the amount of released vancomycin in the solution.

## Early Biofilm Inhibition Study

MRSA is the most common pathogen isolated from the infection site, but other pathogens like *Staphylococcus epidermidis*, coagulase-negative staphylococci, *Enterobacter* species, *Pseudomonas aeruginosa*, and *Mycobacterium* species are also responsible for osteomyelitis. *Staphylococcus aureus* is a gram positive, facultative anaerobe. It has a spherical shape with a 0.5–1.5 μm diameter and forms bead-like clusters when colonized. *S. aureus* is naturally found in human skin and nostrils. It attaches to the surface with its adhesins and exotoxins and many of its strains are capable of forming biofilm (21). Early biofilm inhibition capabilities of vancomycin containing composites discs were evaluated with the tissue culture plate method. A vancomycin containing composite disc from each group ($n$ = 3) was put into a polystyrene tube containing 10 ml of PBS and placed in a hot water bath at 37°C and shaken constantly at 30 rpm. Every week, 1 ml PBS was withdrawn and replaced with an equal amount of fresh PBS until week 6. Each time point was

carried out in triplicate. A slime-forming MRSA strain obtained from Hacettepe University, Faculty of Medicine, Department of Microbiology, was used for this study. Bacterial suspensions were pipetted into sterile glass tubes containing 2 ml of trypticase soy broth (Becton Dickinson, NJ, USA), and the bacterial cultures were set to 0.5 McFarland standard ($1 \times 10^{-8}$ cfu/ml) with a benchtop turbidity meter (Grant Instruments, Cambridge, UK). A 200 µl bacterial suspension was inoculated to fresh 2 ml trypticase soy broth and incubated at 37°C overnight. On another day, bacteria suspension turbidity was checked with a benchtop turbidity meter and the bacteria suspension with 11.0 turbidity was poured into a fresh 48 ml trypticase soy broth. This process was done in duplicate. A 200 µl bacterial culture was added into each well of round bottom 96 well plates (Corning Costar, NY, USA), and 20 µl of drug release media collected from release studies were added to the wells. The plates were incubated at 37°C for 48 h. Trypticase soy broth without any bacteria was used as negative control, while bacterial culture without any release medium was used as positive control.

After incubation, tissue culture plates were turned upside down and the planktonic bacteria were poured out. The plates were washed three times with tap water (200 µl water for each well). After washing, 125 µl 0.1% crystal violet stain was added to each well, and the plates were incubated at room temperature for 10 min. The plates were shaken and the excess stain was poured out; again, the wells were washed twice with water. The plates were placed onto a paper towel and allowed to dry. Each well was filled with 200 µl 95% ethanol, and the plates were incubated at room temperature with closed lids for 15 min. The wells were gently mixed with pipetting, and a 125 µl ethanol-crystal violet mix from each well was placed into a new 96 well plate. The new plates were spectrophotometrically analyzed in ELISA reader (Tecan Sunrise, Mannedorf, Switzerland) at 620 nm.

## *In Vitro* Cell Culture Studies

Composites were evaluated for their proliferation and osteogenic potential in cell culture with hBM-MSCs (passage 6, Lonza, Basel, Switzerland) and SaOS-2 (passage 17, Sigma-Aldrich, MO, USA) cells at days 1, 3, and 7 in triplicate. hBM-MSCs and SaOS-2 cells without any composites were used as control groups. The cells were cultured with the hBM-MSCs or SaOS-2 medium according to cell type. The hBM-MSCs culture medium consisted of 52.8% Dulbecco's Modified Eagle Medium (DMEM) with 1 g/l glucose (Lonza, Basel, Switzerland), 35.2% MCDB-201 medium (Sigma-Aldrich, MO, USA), 10% heat-inactivated fetal bovine serum (FBS; Sigma-Aldrich, MO, USA), 1% penicillin/streptomycin solution (Biochrom AG, Berlin, Germany), and 1% L-glutamine (Biochrom AG, Berlin, Germany), while the SaOS-2 culture medium consisted of 89% DMEM with 4.5 g/l glucose (Sigma-Aldrich, MO, USA), 10% heat-inactivated FBS, and 1% penicillin/streptomycin solution. In every 3–4 days, the media were changed. The assay was done in 24-well cell culture plates (Corning Costar, NY, USA), with analysis for three different time points (on days 1, 3, and 7) in triplicate. In a 24-well cell culture plate, 12 wells were used for MSC, while the other 12 wells were used for SaOS-2 cells. A total of 7,500 cells were seeded on each well and then the composites were placed. The plates were incubated at 37°C with relative humidity under an atmosphere of 5% $CO_2$. At predetermined time points, the medium was aspirated and a 500 µl fresh medium was added with 50 µl of cell proliferation agent WST-1 (Roche, Basel, Switzerland) for each well. The plates were incubated at 37°C with relative humidity under an atmosphere of 5% $CO_2$ for 4 h. After incubation, a 110 µl 1:10 (v/v) WST-1 containing culture medium was pipetted into a flat bottom 96-well plate, and the absorbance of the wells was measured in ELISA reader (Tecan Sunrise, Mannedorf, Switzerland) at 450 nm with 620 nm reference wavelength. Early mineralization potential of the vancomycin containing composites was evaluated with ALP activity staining for hBM-MSCs and SaOS-2 cells. Cells were cultured with the hBM-MSCs or SaOS-2 medium according to the cell type, and on day 21, the medium was discarded and a 400 µl Alkaline Phosphatase Yellow Liquid substrate system for ELISA (Sigma-Aldrich, MO, USA) was added. The plate was incubated for 30 min, and 100 µl of 3 N sodium hydroxide (NaOH) was added to stop the reaction. A 200 µl final product was pipetted to a flat bottom 96-well plate and analyzed with an ELISA reader (Tecan Sunrise, Mannedorf, Switzerland) at 405 nm wavelength.

## qRT-PCR Assay

The hBM-MSCs (total $1.5 \times 10^6$ cells) were cultured in T75 flasks (Corning Costar, NY, USA) with the hBM-MSCs medium at 37°C with relative humidity under an atmosphere of 5% $CO_2$, and in every 3–4 days, the media were refreshed. When the cells reached 60%–70% confluency, culture media in three flasks were discarded and replaced with an osteogenic differentiation medium consisting of 10% FBS, 100 nM dexamethasone, 10 mM ß-glycerophosphate (Applichem, Germany), and 0.2 mM L-ascorbic acid (Sigma-Aldrich, MO, USA) in DMEM-LG. The remaining flasks were used for two different composite discs and extraction media were used for this purpose. Briefly, 33 composite discs from each group were incubated with 30 ml of the hBM-MSCs medium. After 14 days of incubation, the cells were trypsinized with 0.25% Trypsin-Ethylenediaminetetraacetic acid (EDTA) (Invitrogen, Gibco, UK) and suspended in 200 µl PBS. mRNA was isolated with a High Pure RNA Isolation Kit (Roche, Basel, Switzerland) and complementary DNA (cDNA) was synthesized with its kit (Roche, Basel, Switzerland). A 15 µl PCR mix and 5 µl cDNA were pipetted into each well of custom plate designed with different signaling molecules (Roche, Basel, Switzerland). The final PCR reaction was quantified in a Lightcycler 480 and its software was used to calculate the crossing point (*Cp*) for target and reference expression with the Advance Relative Quantification method. All target genes were normalized to housekeeping genes *ACTB* (beta actin), *GAPDH* (glyceraldehyde 3-phosphate dehydrogenase), and *G6PD* (glucose-6-phosphate dehydrogenase). The results were given as fold change corresponding to the hBM-MSCs control group according to $\Delta\Delta Ct$ calculation. The sequences of primers are given in **Table 1**.

**TABLE 1** | Sequences of primers.

| Gene name | Gene description | Forward primer sequence | Reverse primer sequence |
|---|---|---|---|
| *ALPL* | Alkaline phosphatase, liver/bone/kidney | AGAACCCCAAAGGCTTCTTC | CTTGGCTTTTCCTTCATGGT |
| *ANXA5* | Annexin A5 | TCTTCGGAAGGCTATGAAAGG | GGGATGTCAACAGAGTCAGGA |
| *BGLAP* | Bone gamma-carboxyglutamate (gla) protein | CCAGCCCTATGGATGTGG | TTTTCAGATTCCTCTTCTGGAGTT |
| *BMP1* | Bone morphogenetic protein 1 | TATGTGGAGGTCCGAGATGG | GAGTTTGGACCCGCAGAA |
| *BMP2* | Bone morphogenetic protein 2 | GACTGCGGTCTCCTAAAGGTC | GGAAGCAGCAACGCTAGAAG |
| *BMP3* | Bone morphogenetic protein 3 | CCCAAGTCCTTTGATGCCTA | TCTGGATGGTAGCATGATTTGA |
| *BMP4* | Bone morphogenetic protein 4 | GAGGAAGGAAGATGCGAGAA | GCACTACGGAATGGCTCCT |
| *CDH11* | Cadherin 11, type 2, | CATCGTCATTCTCCTGGTCA | TCAAAGACAATGAGTGGTTCTTTC |
| *COL10A1* | Collagen, type X, alpha 1 | CAGTTCTTCATTCCCTACACCA | AGGACTTCCGTAGCCTGGTT |
| *COL14A1* | Collagen, type XIV, alpha 1 | GACCCCTCATCATGTTCTGC | ATGGCTTCCAGCTCATCTTG |
| *COL15A1* | Collagen, type XV, alpha 1 | TGATGGTCGAGACATAATGACA | GGAGCCATGCCAAATGAC |
| *COL1A1* | Collagen, type I, alpha 1 | AGGTGAAGCAGGCAAACCT | CTCGCCAGGGAAACCTCT |
| *COL1A2* | Collagen, type I, alpha 2 | TCTGGAGAGGCTGGTACTGC | GAGCACCAAGAAGACCCTGA |
| *COL2A1* | Collagen, type II, alpha 1 | TTTCAAGGCAATCCTGGTG | TCCAGGTTTTCCAGCTTCAC |
| *COL3A1* | Collagen, type III, alpha 1 | ACTGGAGCACGGGGTCTT | TCCTGGTTTCCCACTTTCAC |
| *COL5A1* | Collagen, type V, alpha 1 | TCTTGGCCCAAAGAAAACC | GGCGTCCACATAGGAGAGC |
| *COMP* | Cartilage oligomeric matrix protein | GGGTCCCCAATGAAAAGG | CCTTTTGGTCGTCGTTCTTC |
| *CTSK* | Cathepsin K | CGAAGCCAGACAACAGATTTC | AGAGCAAAGCTCACCACAGG |
| *EGF* | Epidermal growth factor | CCTCAGATGGGAAAACGTG | GTTCTTTAGATCAACTTCACCACCT |
| *EGFR* | Epidermal growth factor receptor | CAGCCACCCATATGTACCATC | AACTTTGGGCGACTATCTGC |
| *FGF1* | Fibroblast growth factor 1 (acidic) | AATCAGCCAAAGAGCCTGTC | CAAAACAGAGCAGGGAACTACC |
| *FGF2* | Fibroblast growth factor 2 (basic) | CCCGACGGCCGAGTTGAC | CACATTTAGAAGCCAGTAATCT |
| *FGFR1* | Fibroblast growth factor receptor 1 | AAGATTGGCCCAGACAACC | GCACCTCCATCTCTTTGTCG |
| *FGFR2* | Fibroblast growth factor receptor 2 | GACCCAAAATGGGAGTTTCC | GACCACTTGCCCAAAGCA |
| *IGF1* | Insulin-like growth factor 1 | TGCTTTTGTGATTTCTTGAAGG | GCAGAGCTGGTGAAGGTGA |
| *IGF1R* | Insulin-like growth factor 1 receptor | TCAGCGCTGCTGATGTGT | GGCTCATGGTGATCTTCTCC |
| *IGF2* | Insulin-like growth factor 2 | GCTGGCAGAGGAGTGTCC | GGGATTCCCATTGGTGTCT |
| *ITGB1* | Integrin, beta 1 (fibronectin receptor, antigen CD29 includes MDF2, MSK12) | CTTGGAACAGATCTGATGAATGA | TCCACAAATGAGCCAAATCC |
| *MMP2* | Matrix metallopeptidase 2 | TATTTGATGGCATCGCTCAG | ACAGTCCGCCAAATGAACC |
| *MMP8* | Matrix metallopeptidase 8 | GGGAACGCACTAACTTGACC | TTCAAAGGCATCCTTGATAGC |
| *PHEX* | Phosphate regulating endopeptidase homolog, X-linked | AGTGCATCCACCAACCAGAT | TTCCCCAAAAGAAAGGCTTC |
| *RUNX2* | Runt-related transcription factor 2 | GCCTAGGCGCATTTCAGAT | CTGAGAGTGGAAGGCCAGAG |
| *SMAD1* | SMAD family member 1 | TGTGTACTATACGTATGAGCTTTGTGA | TAACATCCTGGCGGTGGTA |
| *SMAD2* | SMAD family member 2 | AAAGGGTGGGGAGCAGAATA | GAAGTTCAATCCAGCAAGGAGT |
| *SMAD3* | SMAD family member 3 | GCATGAGCTTCGTCAAAGG | AATCCAGCAGGGGGTACTG |
| *SMAD4* | SMAD family member 4 | TGGCCCAGGATCAGTAGGT | CATCAACACCAATTCCAGCA |
| *SOX9* | SRY (sex-determining region Y)-box 9 | TACCCGCACTTGCACAAC | TCTCGCTCTCGTTCAGAAGTC |
| *TGFB1* | Transforming growth factor, beta 1 | ACTACTACGCCAAGGAGGTCAC | TGCTTGAACTTGTCATAGATTTCG |
| *TGFB2* | Transforming growth factor, beta 2 | GAAGAACTAGAAGCAAGATTTGCAG | TGATCACCACTGGTATATGTGGA |
| *TGFB3* | Transforming growth factor, beta 3 | GCTTTGGACACCAATTACTGC | CCCAGATCCTGTCGGAAGT |
| *TGFBR1* | Transforming growth factor, beta receptor 1 | AAATTGCTCGACGATGTTCC | CATAATAAGGCAGTTGGTAATCTTCA |
| *TGFBR2* | Transforming growth factor, beta receptor II | GACCAGAAATTCCCAGCTTCT | CAACGTCTCACACACCATCTG |
| *TWIST1* | Twist homolog 1 (Drosophila) | AGCTACGCCTTCTCGGTCT | TCCTTCTCTGGAAACAATGACA |
| *VDR* | Vitamin D (1,25-dihydroxyvitamin D3) receptor | CTTCTCTGGGGACTCCTCCT | TGGACGAGTCCATCATGTCT |
| *HPRT1* | Hypoxanthine phosphoribosyltransferase 1 | TGACCTTGATTTATTTTGCATACC | CGAGCAAGACGTTCAGTCCT |

(*continued*)

**TABLE 1** | Continued

| Gene name | Gene description | Forward primer sequence | Reverse primer sequence |
|---|---|---|---|
| *GDF10* | Growth differentiation factor 10 | TGAATGGATAATCTCACCGAAA | GTTGGATGGACGAACGATCT |
| *ACTB* | Actin, beta | GGCCAGGTCATCACCATT | GGATGCCACAGGACTCCAT |
| *GAPDH* | Glyceraldehyde-3-phosphate dehydrogenase | CTCTGCTCCTCCTGTTCGAC | ACGACCAAATCCGTTGACTC |
| *G6PD* | Glucose-6-phosphate dehydrogenase | TCCATCAGTCGGATACACACA | CACCAGATGGTGGGGTAGAT |
| Control | Polymerase (RNA) II (DNA directed) polypeptide A, 220 kDa | CCTGAGTCCGGATGAACTG | GCCTCCCTCAGTCGTCTCT |
| Control | Polymerase (RNA) II (DNA directed) | GCAAATTCACCAAGAGAGACG | CACGTCGACAGGAACATCAG |
| Control | Polymerase (RNA) II (DNA directed) polypeptide A, 220kDa | TCCGTATTCGCATCATGAAC | TCATCCATCTTGTCCACCAC |
| Control | Transferrin receptor (p90, CD71) | TGGGTTTTTGTTACCTTTATGGTT | GGAGGTAACATGCAAATAATGTGA |
| Control | Transferrin receptor (p90, CD71) | TGGGTTTTTGTTACCTTTATGGTT | GGAGGTAACATGCAAATAATGTGA |

## Statistical Analysis

All results were presented as average ± standard deviation and analyzed with SPSS 11.0. Statistically significant values were defined as $p < 0.05$ based on Student's *t*-test. For determining the significance of the expression fold changes between the groups, the binary logarithm of the $\Delta\Delta Ct$ values was calculated and ±two-fold changes were assigned as significant for the qRT-PCR study. The significant values are indicated in gray boxes in **Table 2**.

# RESULTS

## Composite Characterization

The surfaces of the composites contained micro cracks. The surface properties of the PDLLA/β-TCP and the PLGA/β-TCP composites were similar (**Figure 2**).

The adsorption bands of vancomycin were recorded at 3,252, 1,644, 1,487, 1,225, 1,014, and 426 cm−$^{1}$. The adsorption band at 3,252 cm$^{-1}$ was for O–H stretching, while 1,644 cm$^{-1}$ showed C=O stretching. The bands at 1,487 and 1,225 cm$^{-1}$ pointed at C=C band and C–O–C band, respectively (22). The adsorption bands of β-TCP were found at 1,212 cm$^{-1}$ (the pyrophosphate CPP group band), 1,017 cm$^{-1}$ (C–O stretching), 727 cm$^{-1}$ (P–O stretching), and 542 cm$^{-1}$ (P–O bending) (23). The characteristic peaks of PDLLA and PLGA were found at 1,746 cm$^{-1}$ (C=O band), 1,183 cm$^{-1}$ (C–O band), 1,022 cm$^{-1}$ (C–O band), and 540 cm$^{-1}$ (C–H band) (24). The peaks were recorded at 1,749 cm$^{-1}$ (C=O band), 1,017 cm$^{-1}$ (C–O band), and 538 cm$^{-1}$ in both vancomycin containing composites. The similarities of spectra were pointed in circles; the color red defined vancomycin, green defined β-TCP, purple defined PDLLA, and blue defined PLGA (**Figure 3**).

## Vancomycin Releasing Capacity of Composites

Both PDLLA/β-TCP and PLGA/β-TCP composites maintained a sustained release of vancomycin for 6 weeks. The PDLLA/β-TCP composites released 2.3 ± 0.2 mg vancomycin, while the PLGA/β-TCP composites released 2.1 ± 0.2 mg in a day. After 6 weeks, cumulatively, 3.1 ± 0.2 and 3.4 ± 0.4 mg vancomycin were released from the PDLLA/β-TCP and the PLGA/β-TCP composites, respectively (**Figure 4**).

## Early Biofilm Inhibition Capacity

In the biofilm inhibition study, there was a statistically significant difference between the composite groups and the bacterial control ($p < 0.05$). Released medium added to the bacterial suspensions inhibited early biofilm formation throughout 6 weeks (**Figure 5**).

## Cell Proliferation Capacity

Cells cultured on the composites proliferated, and there was a statistically significant difference for the PDLLA/β-TCP group between day 1 and day 7 for both cell lines ($p = 0.01$ for hBM-MSCs and $p = 0.03$ for SaOS-2, respectively). On the contrary, the PLGA/β-TCP group only showed a statistically significant difference between day 1 and day 7 for the SaOS-2 cell line ($p = 0.03$). Both composite groups showed a statistically significant difference versus blank hBM-MSCs on day 7 ($p = 0.01$), but there was no such significant difference for SaOS-2. There was no statistically significant difference between the groups for day 1 to day 3 or for day 3 to day 7 (**Figure 6**).

## Early Mineralization Potential of the Composites with ALP

PDLLA/β-TCP ($p = 0.011$) and the PLGA/β-TCP ($p = 0.006$) composites cultured with SaOS-2 cells presented a higher ALP activity compared with the SaOS-2 cell group without any composite. The ALP activity of the composites cultured with hBM-MSCs, however, was higher but was not statistically significant than the hBM-MSCs group (**Figure 7**).

## Osteogenic Capacity of the Cells Grown Together with Composites with qRT-PCR

The alkaline phosphatase (ALPL) upregulated 3.44-fold higher in the osteogenic medium group, while it downregulated in composite groups according to control. This downregulation, however, was statistically not significant. Bone morphogenetic protein-1 (BMP-1) upregulated significantly only in the

**TABLE 2 |** The upregulation or downregulation of genes in the test groups according to control.

| | Fold up- or down-regulation according to control | | |
|---|---|---|---|
| **Gene** | **Osteogenic Medium + hBM-MSCs** | **PDLLA/β-TCP + hBM-MSCs** | **PLGA/β-TCP + hBM-MSCs** |
| *ALPL* | 3.44 | −1.36 | −0.37 |
| *ANXA5* | 0.17 | −1.11 | −0.73 |
| *BGLAP* | 1.33 | −0.06 | 0.69 |
| *BMP1* | 2.11 | −0.10 | 0.52 |
| *BMP2* | 1.78 | 2.18 | 3.36 |
| *BMP3* | −1.29 | −2.31 | −1.12 |
| *BMP4* | 0.49 | −1.16 | −0.98 |
| *CDH11* | −0.09 | −0.88 | −0.56 |
| *COL10A1* | 1.60 | 0.93 | 3.09 |
| *COL14A1* | −2.06 | −0.79 | −0.70 |
| *COL15A1* | −1.05 | 0.65 | 1.65 |
| *COL1A1* | 0.13 | 0.80 | 1.11 |
| *COL1A2* | 0.56 | 0.16 | 0.46 |
| *COL3A1* | 1.26 | 0.34 | 0.68 |
| *COL5A1* | −0.89 | −0.17 | 0.11 |
| *COMP* | 3.51 | 1.19 | 2.55 |
| *CTSK* | 2.41 | 0.49 | 1.14 |
| *EGF* | −0.46 | −1.37 | −1.20 |
| *EGFR* | −0.41 | −1.23 | −1.36 |
| *FGF1* | −0.59 | −0.57 | −0.10 |
| *FGF2* | −2.85 | −0.74 | −1.17 |
| *FGFR1* | 0.35 | −0.03 | 0.19 |
| *FGFR2* | −0.60 | −0.70 | −0.54 |
| *IGF1* | 0.76 | 1.93 | 2.53 |
| *IGF1R* | 0.13 | −1.18 | −1.19 |
| *IGF2* | 3.63 | −1.72 | −0.94 |
| *ITGB1* | −0.11 | −0.90 | −0.63 |
| *MMP2* | 0.19 | 0.67 | 1.17 |
| *MMP8* | 5.72 | 1.12 | 1.82 |
| *PHEX* | 0.75 | −2.91 | −1.01 |
| *RUNX2* | 1.34 | −0.60 | −0.43 |
| *SMAD1* | 0.45 | −2.26 | −1.01 |
| *SMAD2* | 0.17 | −0.87 | −0.57 |
| *SMAD3* | −1.26 | −1.14 | −1.66 |
| *SMAD4* | 0.30 | −0.58 | −0.44 |
| *SOX9* | −1.38 | 0.01 | −0.14 |
| *TGFB1* | 0.27 | 0.86 | 1.28 |
| *TGFB2* | 0.51 | −1.74 | −2.39 |
| *TGFB3* | 1.07 | 0.20 | 0.89 |
| *TGFBR1* | −5.17 | −4.85 | −4.41 |
| *TGFBR2* | 1.30 | −0.51 | −0.26 |
| *TWIST1* | 0.85 | 0.35 | −0.54 |
| *VDR* | −0.59 | 2.59 | 2.02 |

*PDLLA, poly(D,L-lactide); PLGA, poly(D,L-lactide-co-glycolide); β-TCP, beta-tricalcium phosphate; hBM-MSCs, human bone marrow-derived mesenchymal stem cells.*

osteogenic medium group, while bone morphogenetic protein-2 (BMP-2) was upregulated only in the composite groups. Bone morphogenetic protein-3 (BMP-3) downregulation was statistically significant only for PDLLA/β-TCP. Bone morphogenetic protein-4 (BMP-4) was not expressed significantly in any group. Collagen, type X, and alpha 1 (COL10A1) expressed significantly only in the PLGA/β-TCP group. The cartilage oligomeric matrix protein (COMP) was upregulated in each group, but its expression was significant only in the osteogenic medium and in the PLGA/β-TCP groups. Cathepsin K (CTSK), insulin-like growth factor 2 (IGF2), and matrix metallopeptidase 8 (MMP8) expressions upregulated only in the osteogenic medium group. The expression of insulin-like growth factor 1 (IGF1) increased in all groups, while it was significant for the PLGA/β-TCP group.

SMAD expressions decreased in the composite groups, which were significant only for SMAD1 in the PDLLA/β-TCP group.

Transforming growth factor, beta 2 (TGF-β2), downregulated in the PLGA/β-TCP group, while TGF-βR1 (receptor 1 of TGF-β) downregulated in all groups. Vitamin D receptor (VDR) downregulated in the osteogenic medium group; on the contrary, it was upregulated significantly in the composite groups. RUNX2 upregulated in the osteogenic medium group and downregulated in the composite groups; however, these expressions were not significant (**Table 2**).

## DISCUSSION

MRSA chronic osteomyelitis is a devastating disease with limited cure, including long-term systemic antibiotic administration and repetitive surgeries (25). Poor blood circulation in the infection area and bone necrosis makes osteomyelitis a persistent disease, and treatment can hardly be achieved (26); so, local antibiotic delivery systems are generated (27). Various polymers, calcium-based composites, and manufacturing methods for local drug delivery systems reveal that an optimum system has not yet been produced (28–32). PDLLA, PLGA, and β-TCP are chosen to fabricate the composites since these materials are clinically used for a long time due to their safety and biocompatibility (33, 34). Booysen et al. searched for the cytotoxicity of vancomycin on hBM-MSCs and found that a high amount of vancomycin did not lead to any cytotoxicity as it did not inhibit the osteogenic differentiation (35).

Both PDLLA/β-TCP and PLGA/β-TCP composites released vancomycin for 6 weeks. The composites had smooth surfaces with microcracks. PDLLA/β-TCP composites released only $3.1 \pm 0.2$ mg of its vancomycin, while PLGA/β-TCP composites released $3.4 \pm 0.4$ mg. There was a slight difference between the released amounts, so the type of polymer used in this study did not have an impact on the release properties. On the contrary, the initial burst of vancomycin in 24 h was in line with a previous study (36) and one of the key points in inhibiting early biofilm formation (37). We assumed that this initial burst was related to the diffusion of vancomycin located near the surface of the composites. Since the TCP particles

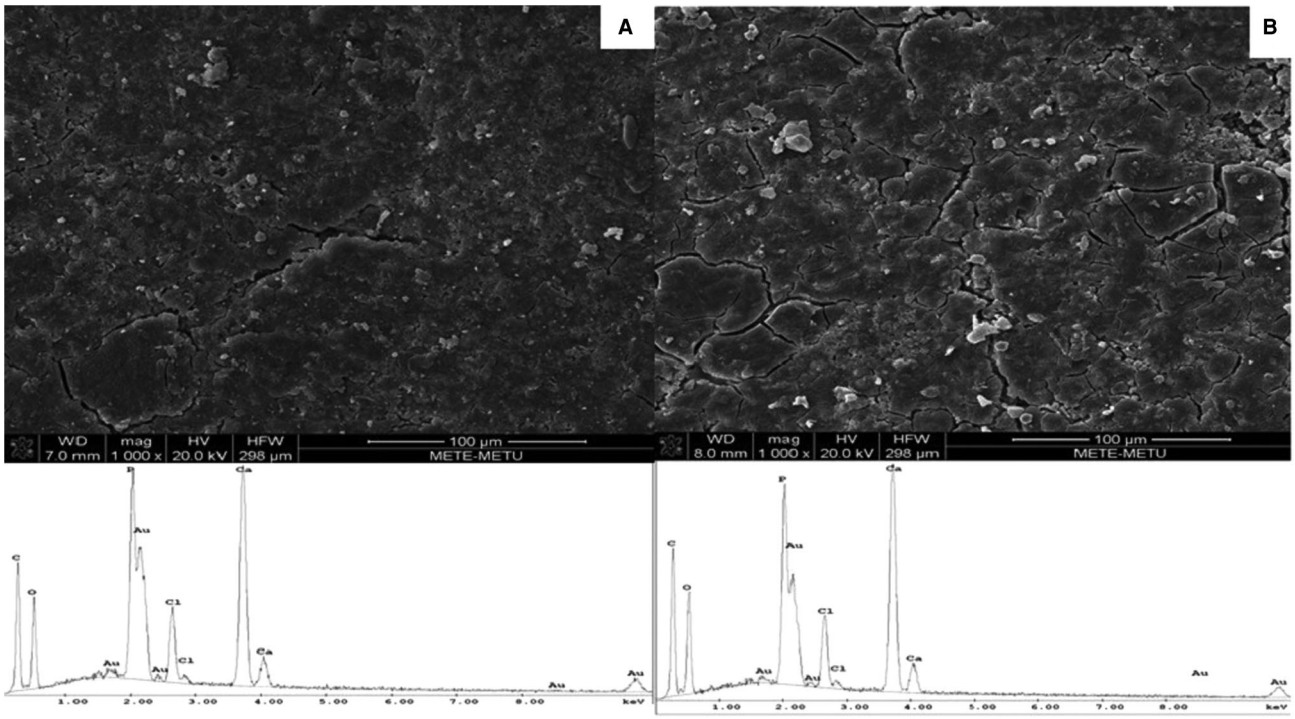


**FIGURE 2** | SEM micrographs (1,000× magnification) and EDS spectra of vancomycin containing (**A**) PDLLA/β-TCP and (**B**) PLGA/β-TCP composites. PDLLA, poly(D,L-lactide); PLGA, poly(D,L-lactide-co-glycolide); β-TCP, beta-tricalcium phosphate; EDS, energy-dispersive spectrometry; SEM, scanning electron microscope.

were only physically blended into the polymer, they occupied random spaces in the polymer. After the composite was immersed in solution, the hydrophilic TCP particles tended to fall off and interact with the surrounding medium. The falling of TCP also created voids within the composite, thus exposing their surfaces to hydrolytic attack and weakening the overall structure.

Crystal violet is a dye that generally binds to biofilm polysaccharides and make biofilm visible (38). According to crystal violet staining results, vancomycin containing PDLLA/β-TCP and PLGA/β-TCP composites were able to inhibit early biofilm formation (39) and, therefore, preventing early biofilm formation was critical in the treatment of osteomyelitis (2). Since the protocol was done with planktonic bacteria, there was no statistically significant difference between the time points.

The proliferation of MSC and SaOS-2 cells with the composites was established, and this finding was in line with previous studies (40, 41) where cells were combined with other biomaterials. However, there was no correlation between the proliferation rate and the topography of the composite surfaces, since the smooth surface structure led to a lower cell proliferation rate with respect to the study conducted by Pulyala et al. (42).

Cells interacted with composites presented more ALP activity than the cells cultured without any composite, but there was no significant difference between the groups for hBM-MSCs. The significant differences in the SaOS-2 cell groups were related to the osteoblast-like nature of the SaOS-2 cells. Since these cells had osteoblast-like properties, it was expected that these cells showed a higher ALP activity than hBM-MSCs (43). Our findings were in line with previous studies (44, 45).

ALPL, however, decreased in the composite groups. The expression of ALPL was low for both composites, but the differences in the fold changes were not significant. The cells cultured with the osteogenic medium showed a higher ALPL expression with regard to the presence of the dexamethasone and ascorbic acid (46) found in the osteogenic medium. BMP1, a secreted metalloprotease requiring calcium and necessary for cartilage and bone formation (47), was significantly upregulated in the osteogenic medium group, opposed to the composite groups. The expression and activation of RUNX2 (48) is regulated by many bone-derived growth factors, including BMPs. BMPs form a unique group of proteins within the TGF-β super family of genes and play pivotal roles in the regulation of cartilage and bone development. BMP-activated SMADs (SMAD1, -5, and -8) induce *RUNX2* gene expression, and SMADs interact physically with the RUNX2 protein to induce osteoblast differentiation (49). In our study, neither BMP1 nor BMP4 was upregulated. Only BMP2 was upregulated with the composites, but this upregulation was not sufficient for inducing the upregulation of SMADs, and consequently, there was no RUNX2 upregulation (50). On the other hand, TGF-β1 upregulated in the composite groups, but this still did not lead to the upregulation of the *SMAD* genes. The

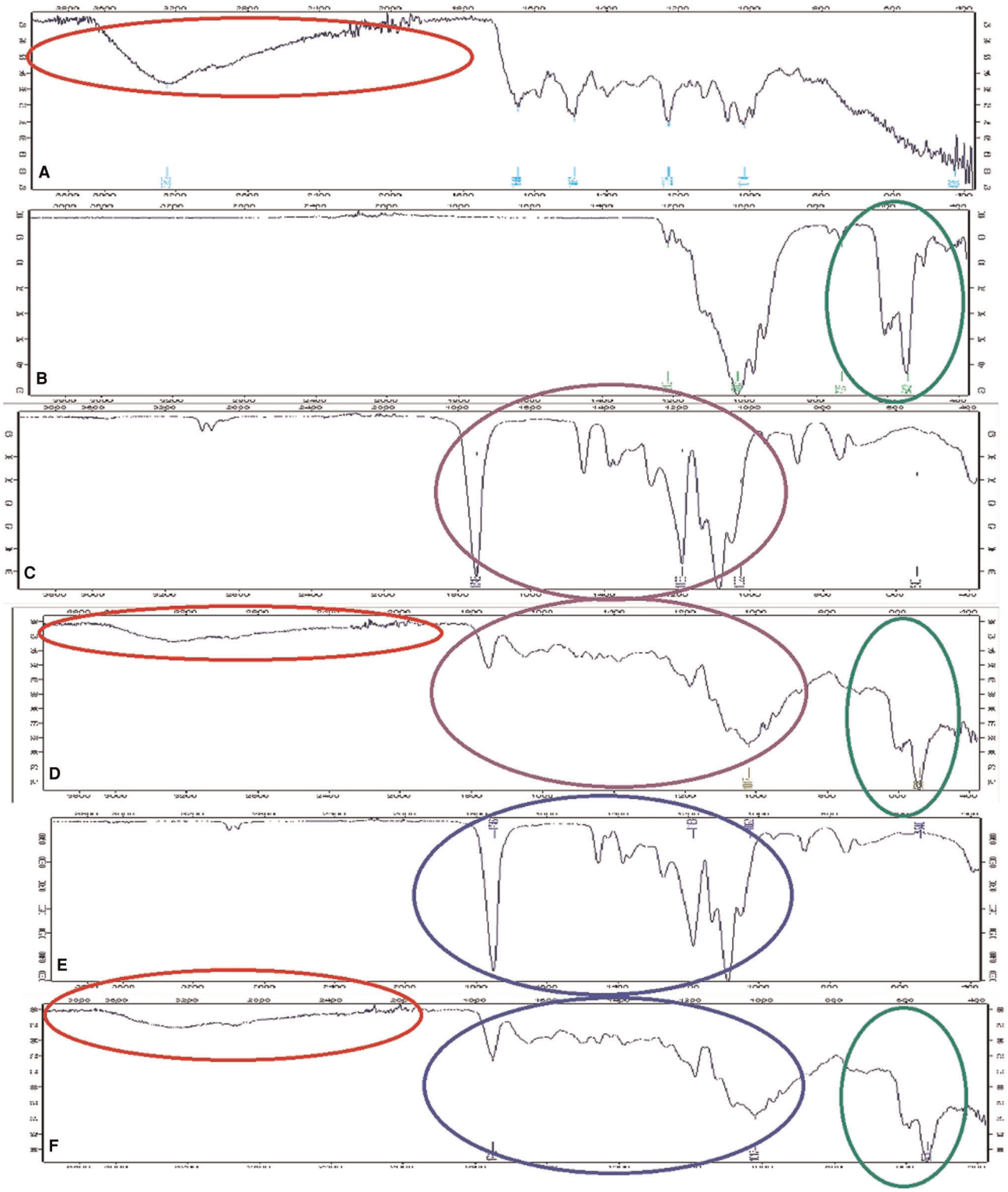


**FIGURE 3** | FTIR spectra of (**A**) vancomycin, (**B**) β-TCP, (**C**) PDLLA, (**D**) vancomycin containing PDLLA/β-TCP composite, (**E**) PLGA, and (**F**) vancomycin containing PLGA/β-TCP composite. PDLLA, poly(D,L-lactide); PLGA, poly(D,L-lactide-co-glycolide); β-TCP, beta-tricalcium phosphate.

upregulation of RUNX2 in the osteogenic medium group, however, had no statistically significant difference when compared with the composite groups. TGF-β2, one of TGF-β isoforms within the bone matrix, modulates the differentiation of osteoblasts and the proliferation of osteoprogenitor cells (51). Here, only the cells cultured with osteogenic differentiation medium showed the upregulation of TGF-β2, but this upregulation was not significant. On the other hand, it was downregulated in the composite groups and, therefore, osteoblastic differentiation of the cells in the composite groups could have been delayed.

Composite groups did not present any osteoinduction activity according to the qRT-PCR studies as they did not cause hBM-MSCs to express a group of osteogenesis-related signaling molecules in the absence of an osteogenic medium (48). In addition, the high content of TCP in the composites may inhibit the expression of some osteogenic markers by hBM-MSCs (52). The composites, thus, showed a higher ALP activity with the colorimetric assay as a sign of mineralization. This could be a feature of high TCP content in the composites (53).

In conclusion, we were able to produce and characterize biocompatible PDLLA/β-TCP and PLGA/β-TCP composites that were sufficiently released vancomycin *in vitro*. These composites inhibited early biofilm formation and allowed MSC and SaOS-2 cell proliferation. Osteogenesis was not achieved as these composites were osteoconductive. Combining these composites

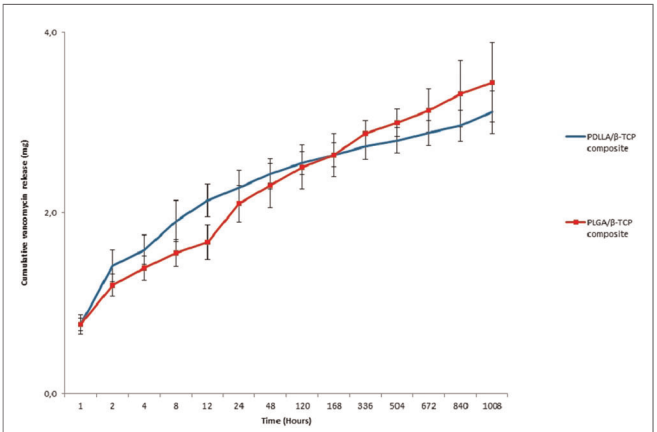


**FIGURE 4** | Cumulative released vancomycin amount from the composites in 6 weeks. PDLLA, poly(D,L-lactide); PLGA, poly(D,L-lactide-co-glycolide); β-TCP, beta-tricalcium phosphate.

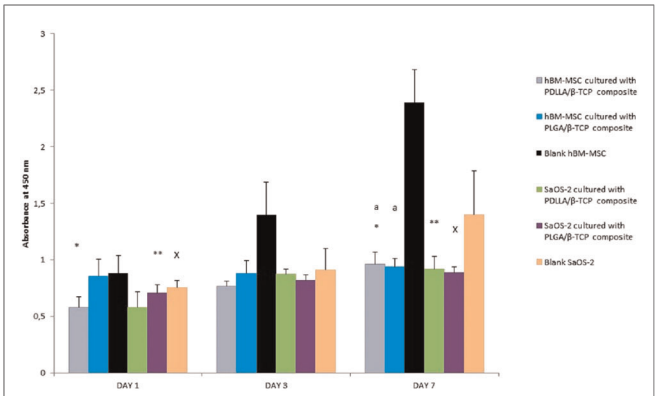


**FIGURE 6** | Proliferation of the MSC and SaOS-2 cells in days 1, 3, and 7 according to the absorbance of WST-1 at 450 nm. PDLLA, poly(D,L-lactide); PLGA, poly(D,L-lactide-co-glycolide); β-TCP, beta-tricalcium phosphate; SaOS-2, osteosarcoma cell; hBM-MSC, human bone marrow-derived mesenchymal stem cell; WST, water soluble tetrazolium salt.

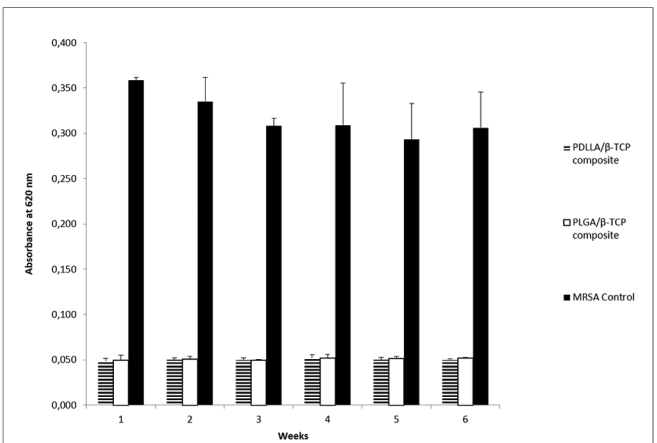


**FIGURE 5** | Absorbance results of bacterial control, PDLLA/β-TCP and PLGA/β-TCP composites at 620 nm (weeks are defining the time point of drug release media collected from release studies). PDLLA, poly(D,L-lactide); PLGA, poly(D,L-lactide-co-glycolide); β-TCP, beta-tricalcium phosphate; MRSA, methicillin-resistant *Staphylococcus aureus*.

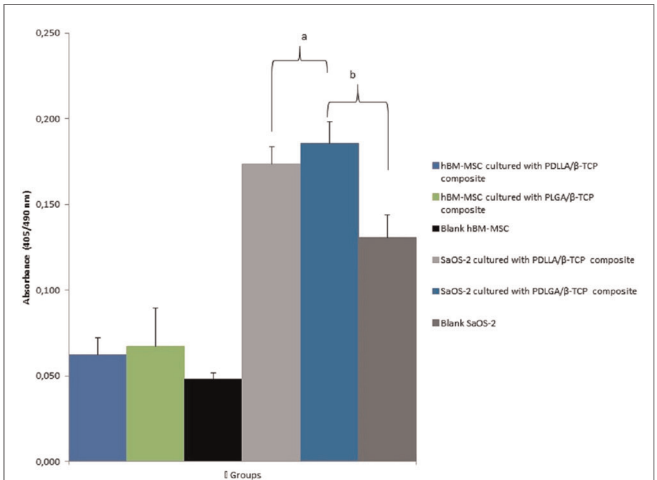


**FIGURE 7** | Alkaline phosphatase (ALP) activity of the groups at day 21 according to their absorbances at 405 nm. PDLLA, poly(D,L-lactide); PLGA, poly(D,L-lactide-co-glycolide); β-TCP, beta-tricalcium phosphate; SaOS-2, osteosarcoma cell; hBM-MSC, human bone marrow-derived mesenchymal stem cell.

with osteogenic active molecules could be a strategy for future studies.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/Supplementary Material; further inquiries can be directed to the corresponding author/s.

## AUTHOR CONTRIBUTIONS

BK, EB, PK, and FK contributed equally to this work. BS contributed to microbiological testing, while HE contributed to the manufacturing of composites. PM contributed to qRT-PCR testing. All authors contributed to the article and approved the submitted version.

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# The application of artificial intelligence in spine surgery

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Due to its obvious advantages in processing big data and image information, the combination of artificial intelligence and medical care may profoundly change medical practice and promote the gradual transition from traditional clinical care to precision medicine mode. In this artical, we reviewed the relevant literatures and found that artificial intelligence was widely used in spine surgery. The application scenarios included etiology, diagnosis, treatment, postoperative prognosis and decision support systems of spinal diseases. The shift to artificial intelligence model in medicine constantly improved the level of doctors' diagnosis and treatment and the development of orthopedics.

KEYWORDS

artificial intelligence, application, spine surgery, machine learing, treatment

## Introduction

As a new subject, artificial intelligence (AI) mainly studies a new technology for imitating and expanding human intelligence. In the past 10 years, AI has made tremendous progress. Machine learning (ML) is a subset of AI that enables algorithms or classifiers to learn large complex data sets and generate useful predictive outputs. More specifically, common applications of ML include classification, regression and clustering. Another way to describe the different forms of ML is based on the nature of the tasks to be performed which include supervised learning, unsupervised learning and reinforcement learning (1). And supervised learning is the most common type of learning used in medical research. The methods used for supervised learning are briefly described in **Table 1**.

This study reviewed the scientific literature from 2007 to 2022 with syntax specific for machine learning and spine surgery applications. Articles not available in the full text were excluded, as well as duplicate articles and those that did not utilize a form of AI or ML pertaining to spine surgery. Specific data was extracted from the available literature including algorithm application, algorithms tested, database type and size, algorithm training method, and outcome of interest. A total of 49 studies met inclusion criteria and our interest. Studies were grouped into five general types: etiology, diagnosis, treatment, postoperative prognosis and decision support systems of spinal diseases. Across studies, a wide swath of algorithms were used, which were trained across multiple disparate databases.

TABLE 1 The methods used for machine learning.

| | Description | Feature |
|---|---|---|
| Linear regression | Fitted by means of the least squares method | Simplicity; Incapability of capturing a nonlinear behavior; Underfitting |
| Logistic regression | Seen as the equivalent of linear regression for classification problems | Multiclass classification problems |
| Bayes classifier | Based on Bayes' theorem of conditional probability | Simplicity |
| Support vector machine | Build the hyperplane, or a number of them, which can divide the space so that the points of the different classes are effectively and optimally partitioned | Multiclass linear classification tasks, including image segmentation; Adapted to nonlinear classification and regression problems |
| Decision trees | Link the values of the features to the possible outputs, therefore implementing a classification or a regression task, by means of a set of conditions | Easier to understand; Suitable for very large datasets |
| Artificial neural networks | Resemble how the neurons are connected and interact in the brain | Reduce the risk of overfitting; Achieve a faster and more robust convergence |
| Convolutional neural networks | Mimic the structure of the animal visual cortex | Image processing; Reduce the risk of overfitting |

As testified by the sharp increase in the number of published papers in recent years, AI and ML are more and more being used in the field of spine surgery (**Figure 1**). Starting from whether the new technology of artificial intelligence can have an impact on the whole process of traditional spinal disease diagnosis and treatment, this paper intends to review the application of artificial intelligence in spinal surgery from the whole process of etiology, diagnosis, treatment, postoperative prognosis and decision support systems of spinal diseases, make use of clinical transformation platform to break through cutting-edge medical technology, standardize the diagnosis and treatment plan of spinal diseases, strive to obtain more original research results with practical application value or theoretical significance, and make contributions to the protection of people's health and safety.

## Etiology

With changes in social lifestyles, the incidence of spinal diseases is increasing. Medical workers have been committed to the etiology of spinal diseases for a long time, because only when the etiology is determined, can we better prevent the occurrence of diseases. In the field of spine surgery, the etiology is often closely related to the patient's personal, environmental, social and other factors. Therefore, the advantage of machine learning in processing large data can better analyze the etiology. For example, as a prevalent degenerative disease of the cervical spine, the trend of the loss of the physiological cervical spine curve has not been fully defined across gender and age groups. In 2020, Shin (2) used an automated deep learning system (DLS) to conduct a population-based large-scale epidemiological study of cervical curvature. Lateral radiographs of 13,691 patients were analyzed with automatic cervical spine segmentation, From 2006 to 2018, the decline in the lordosis curve was prominent in both men and women under 70 years of age and in age groups, and the decline was more remarkable in women and the younger. This rapid decline for women might be related to the increase in mobile-centric environments over the past decade and the increase in smartphone addiction (3). Further studies are needed to assess the association between neck pain and loss of cervical lordotic curve to meet the need for neck postural correction.

Electronic medical record systems are a key source of medical data, generating large and expanding data sets. Rich data stored in electronic medical record system and computer processing power are in good agreement with the development of artificial intelligent technology, in the future, spine disease etiology analysis will more come from patients' electronic health records database or national health insurance database. Due to the processing ability of artificial intelligence to huge data, the etiology can be better analyzed, so as to achieve the early intervention of pathogenic factors and provide help for follow-up treatment.

## Diagnosis (based on imaging)

Medical imaging plays an important role in the diagnosis and treatment of spinal diseases. Automatic detection, classification and location of disease in medical images are significant tasks to support clinical decision. The increasing burden of spinal disease related to an aging population and the increasing availability of magnetic resonance imaging (MRI) and computed tomography (CT) scans have led to a significant increase in radiological data related to the spine. Artificial intelligence (AI) and machine learning (ML) technologies have also made significant advances in recent years, automated analysis capabilities of machine learning models can quickly generate quantitative parameters from image data, which will reduce radiologists' workload. In fact, for the analysis of spinal imaging data, locating anatomical structures in the imaging data is usually the first step in the progress of fully automated analytical methods for detecting,

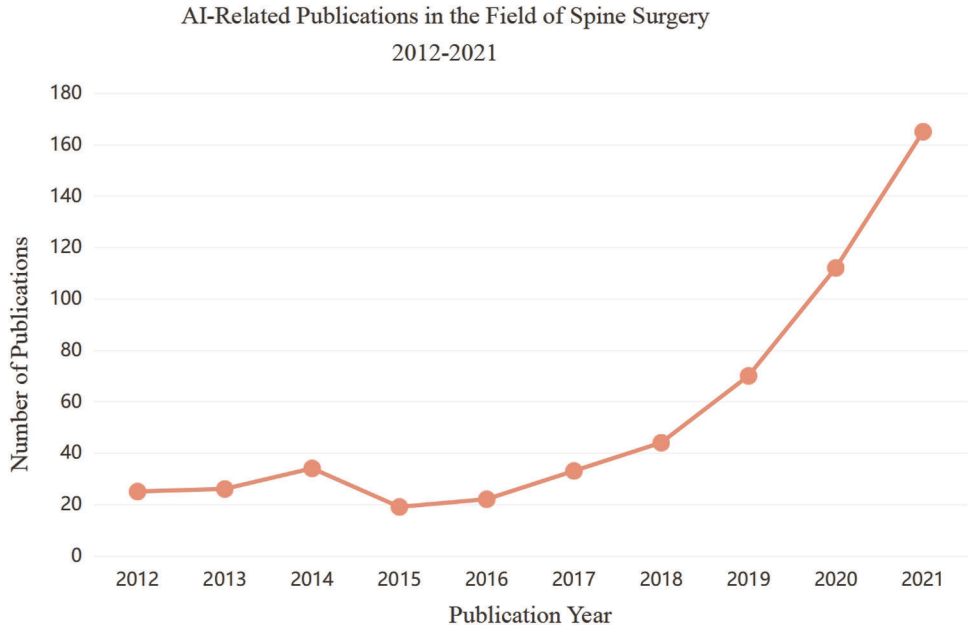


FIGURE 1
AI-related publications in the field of spine surgery 2012–2021.

classifying, or predicting pathological features. For example, Schmidt (4) uses the classification tree method to produce the probability map of the centroid position of each intervertebral disc in MRI images, and then uses the probability map model to infer the most likely position of the intervertebral disc centroid. Compared with manual measurement, the average positioning error is 6.2 mm. Oktay and Akgul (5) trained the model for disc localization using support vector machine (SVM) and achieved an average positioning error of 2.6–3.6 mm based on disc level. At the same time, the author also improved the method to locate the vertebral body, and achieved an average positioning error of less than 4 mm (6). Glocker (7, 8) used the random forest method to establish a model for locating the vertebral body in CT images with an average positioning error of 6–8.5 mm, thus solving the difficult problems of locating the vertebral body in CT images of pathological spinal diseases, including serious scoliosis, sagittal deformity and the presence of internal fixation. Recently, artificial neural network and deep learning have also been used to locate spinal structures. Chen (9) established an artificial neural network model to predict the intervertebral disc centroid, making the average positioning error reduce to 1.6–2 mm, which is a significant improvement over previous models not based on deep learning. In 2021, Suri (10) developed a deep learning system that can automatically and fastly segment vertebral body and discs in MR, CT, and x-ray imaging studies. The model was able to produce median Dice scores >0.95 in all modalities for vertebral bodies and intervertebral discs. Radiomic features calculated from predicted segmentation masks were highly accurate ($r \geq 0.96$ across all radiomic features when compared to ground truth). Mean time to produce outputs was <1.7 s in all modalities. The model can be immediately used in radiological and clinical imaging studies to assess spinal disease, because it can quickly produce the output of these commonly used modalities. The most advanced technology for locating and mapping spinal structures on imaging are now comparable to those of human experts.

In the future, ML models may combine clinical information with quantitative parameters from patient imaging information, such as patient demographic information and neurological examination. It can provide decision making to clinicians. This decision tool uses machine learning technology to determine which patients will benefit from surgery and help with surgical planning. This has led to a quick increase in research connected with computer-assisted spinal imaging analysis (**Table 2**).

## Proposing new classification

The level of heterogeneity of clinical feature and treatment options for adult spinal deformity (ASD) is one of the most important features of the condition. There is a lack of an objective classification to guide which patients with ASD may benefit most from surgical treatment and which surgical treatment is likely to yield the best results. In 2019, Ames (20) proposed artificial intelligence-based (AI) hierarchical

TABLE 2 AI and ML in the diagnosis of spinal diseases.

| Author | Models | Dataset | Type of outcome | Result |
|---|---|---|---|---|
| Schmidt et al. (4) | Probability map | 16 images | Intervertebral disc centroid | Average positioning error 6.2 mm |
| Oktay et al. (5) | SVM | 40 subjects/240 discs | Disc localization | Average positioning error 2.6–3.6 mm |
| Oktay et al. (6) | SVM | 80 subjects/400 lumbar vertebrae | Vertebral body | Average positioning error less than 4 mm |
| Glocker et al. (7) | Random forest | 200 CT scans | Vertebral body | Average positioning error 6–8.5 mm |
| Glocker et al. (8) | Random forest | 424 CT scans | Vertebrae localization | Average positioning error 6–8.5 mm |
| Chen et al. (9) | ANN | 35 patients/245 discs | Intervertebral disc centroid | Average positioning error 1.6–2 mm |
| Suri et al. (10) | ANN | 1,123 MR, 137 CT, 484 x-ray | Vertebral bodies and intervertebral discs | Median Dice scores >0.95 |
| Carson et al. (11) | CNN | 50 subjects | Detect anatomic structures | Mean Dice coefficient score for each tissue type was >80% |
| Galbusera et al. (12) | CNN | 493 patients | Predict spine shape | 2.7°–11.5° |
| Korez et al. (13) | CNN | 55 subjects/97 images | Parameters of the sagittal spinopelvic balance | No statistically significant differences |
| Yeh et al. (14) | CPN | 2,210 images | Anatomic landmarks | Matches the reliability of doctors for 15/18 |
| Wu et al. (15) | MVC-Net | 154 patients/526 images | Adolescent Idiopathic Scoliosis (AIS) | 4.04° CMAE in AP Cobb angle and 4.07° CMAE in LAT Cobb angle |
| Tomita et al. (16) | CNN | 1,432 CT scans | Extract radiological features | Accuracy of 89.2% and an F1 score of 90.8% |
| Fang et al. (17) | DCNN | 1,449 patients | Vertebral segmentation and bone mineral density | The minimum average dice coefficients for three testing sets were 0.823, 0.786, and 0.782 |
| Jamaludin et al. (18) | CNN | 2,009 patients/12,018 discs | Lumbar MRI radiographic grading | Close to human performance |
| Yabu et al. (19) | CNN | 814 patients/1,624 slices | Osteoporotic Vertebral Fracture (OVF) | AUC 0.949 |

clustering as a step in a classification scheme to optimize the overall quality, value, and safety of ASD surgery. The study analyzed 570 patients, identified three optimal patient types and four surgical clusters, and the clusters based on patient characteristics and surgical clusters generated 12 subgroups, SRS-22, ODI, SF-36 and the incidence of complications in each subgroup were analyzed 2 years after surgery to enhance preoperative decision-making. In addition, pattern recognition can be treated by education surgeon which patterns can be obtained under the condition of the lowest risk best improve, thereby promoting treatment optimization. In 2021, Durand et al. (21) used an unsupervised self-organizing neural network to classify the overall sagittal spinal and pelvic morphology of adult spinal malformations based solely on sagittal spinal images and independent of pre-measured angles. The study classified 915 adult patients who had preoperative lateral radiographs. The mean spinal shape of six clusters was plotted and found to be correlated with sagittal plane parameters, baseline levels, and operation characteristics. The relationship between sagittal vertical axis (SVA) and proximal junctional kyphosis (PJK) varies with clusters. This study illustrates the value of analyzing the overall spinal shape of all spinal pelvic structures rather than isolated metrics between selected structures. This study represents a major advance in integrating computer vision into a clinically relevant classification system for adult spinal malformations.

## Improving diagnosis rate

### Based on the ultrasound imaging

Current methods for intraoperative localization and visualization of nerve structures within the psoas muscle are limited and may affect the safety of lateral lumbar interbody fusion (LLIF). The ultrasonic technology enhanced by neural detection algorithm based on artificial intelligence can be used in this work. In 2021, Carson (11) developed image processing and machine learning algorithms using an *in vivo* pig model (50 subjects), and used an ultrasound imaging system to detect the internal and adjacent nerves and other anatomical structures of the lumbar muscle during lateral lumbar surgery. The imaging system's ability to detect and classify anatomical structures was evaluated in subsequent tissue dissection. The mean Dice coefficient score for each tissue type was >80%, the mean specificity of nerve detection was 92%; for bone and muscle, it was >95%.

The accuracy of nerve detection was >95%. AI-enhanced ultrasound imaging can provide the important anatomical structures near the visual figure, so as to provide the surgeon with aims to improve the security of key information LLIF surgery.

## Based on the x-ray

Manual measurement and calculation of a large number of spinal and pelvic parameters on whole spine radiographs in a clinical setting requires considerable time and effort. Therefore, semi-automatic or automatic locating of spinal radiographic anatomical markers and vertebral segmentation on radiographs have been explored for more than ten years. Recently, deep learning has been applied to automatic sagittal imaging parameters measurement, and has good correlation with manual measurement (12, 13, 15, 22, 23). It is worth mentioning that there are ways to better represent spinal alignment because they can evaluate multiple spinal pelvic parameters at once. For example, Galbusera et al. (12) trained 78 different deep learning models to derive 78 anatomical coordinates and six pelvic parameters. Korez et al. (13) could first detect four anatomical structures and then derive five anatomical markers within the detected structures. However, these models may not be able to recognize between similar adjacent anatomical structures, the imaging parameters predicted are not comprehensive enough to cover the entire spinal and pelvic structures, or some of these studies (13, 24–26) often involve segmentation of the image into small pieces and may lose the ability to utilize all relevant anatomical structures of the entire image. For pathological spine images, test data sets are often inadequate in number and diversity, and they may not represent a true clinical picture. Yeh et al. (14) created a dataset of 2,210 radiographs, which is the biggest annotated dataset of all kinds of pathological spine to date. The deep learning model constructed uses the anatomical structure of the entire x-ray film to predict anatomical coordinates and generates various radiological parameters that are well correlated with manual measurements.

In 2018, Wu et al. (15) put forward a new Multi-View Correlation Network (MVC-NET) architecture which can provide a fully automated end-to-end framework for assessing Adolescent Idiopathic Scoliosis (AIS) in multi-view (AP and LAT) x-rays. The results of the experiment on 526 x-ray images from 154 patients indicate an impressive 4.04° Circular Mean Absolute Error (CMAE) in AP Cobb angle and 4.07° CMAE in LAT Cobb angle estimation, which shows the MVC-Net's capability of robust and accurate estimation of Cobb angles in multi-view x-rays. It provides clinicians with an effective, accurate and reliable framework for assessing spinal curvature for comprehensive AIS assessment.

## Based on the CT

Osteoporosis is characterized by loss of bone mass and damage to bone structure, leading to osteoporosis and deeply increasing the risk of fractures. Fractures caused by osteoporosis are emerging as a primary health issues for the elderly (27) causing severe personal suffering and a social and economic burden. The current clinical standard for assessing fracture risk is Bone Mineral Density (BMD) by Dual x-ray Absorbtiometry (DXA) combined with clinical risk factors. However, less than half of fracture patients are clinically diagnosed with osteoporosis by BMD test (28). In addition to the DXA, other imaging methods have been used to identify fractures in high-risk individuals, including CT-based volumetric BMD and geometry (29, 30) and finite element analysis of CT images (31–33). There are endless researches on CT image analysis and modeling using machine learning method to predict fracture caused by osteoporosis. In 2018, Tomita et al. (16) used a deep convolutional neural network (CNN) to extract radiological features from each slice of CT scan. These extracted features are processed by feature aggregation modules for final diagnosis on full CT scans and detection of OVF at the licensed radiologist level for sporadic CT examinations of the chest, abdomen, and pelvis. Based on the test results of 129 CT scans, the accuracy of the system was 89.2% and the F1 score was 90.8%. This automated detecting system could potentially reduce the time and labor load of radiologists screening for osteoporotic vertebral fractures and reduce the potential for false negative results in the early diagnosis of asymptomatic vertebral fractures. The system can also help improve the diagnosis of osteoporotic vertebral fractures in a clinical setting by pre-screening routine CT examinations and flagging suspicious cases prior to the radiologist's examination. In 2021, Fang et al. (17) applied deep learning to patients with primary osteoporosis and explored an automatic model based on deep convolutional neural network (DCNN), which is used for vertebral segmentation and bone mineral density calculation in CT images. Deep learn-based methods can realize automatic identification of osteoporosis, osteopenia and normal bone mineral density in CT images, which is helpful for clinicians to screen and diagnose opportunistic osteoporosis in CT scans of spine or abdomen.

## Based on the MRI

In 2017, Jamaludin et al. (18) analysed 12,018 discs in 2,009 patients using a convolutional neural network without a separate segmentation step prior to classification, using disc volume as input and training only on specific disc classification labels to automatically generate lumbar MRI radiographic grading. In this model, the classification of lumbar disc degeneration, disc stenosis, upper/lower marrow changes, spondylolisthesis, and central canal stenosis has

achieved close to human performance. On the basis of the work, DeepSPINE Framework took advantage of a great dataset of 22,796 lumbar disc herniated segments to train a convolutional neural network and grade spinal and foraminal stenosis in a multi-task mode in 2018. The studies were more accurate in the classification of lumbar spinal stenosis (84.5%) and lumbar foraminal stenosis (89.0%) than any other published study. Furthermore, the DeepSPINE framework performed equally to human evaluators in detecting and grading lumbar spinal stenosis and foraminal stenosis. In 2021, Yabu et al. (19) constructed nine neural network models to detect fresh osteoporotic vertebral fractures and constructed an optimal model using an integrated approach. Tools for automated detection of osteoporotic cone fractures have previously been reported (16). However, these tools only assess the existence of osteoporotic vertebral fractures on CT images, not the freshness of the fractures In this study, 1,624 T1-weighted MRI images from 814 patients with fresh osteoporotic vertebral fractures were used to train and verify the model. Finally, the area under ROC curve (AUC) was 0.949. The diagnostic accuracy, specificity and sensitivity of the model were comparable to those of two independent doctors.

In most instances artificial intelligence cannot directly apply the text image generated by radiology department. Medical reports are usually unstructured text in natural language, but they are difficult to access and are not suitable for annotation in artificial intelligence model training and testing. Most studies using deep learning techniques to identify spinal parameters have been recorded, but their accuracy and consistency are limited compared with human behavior. At the same time, the graphics technology related to spinal image is mainly committed to developing segmentation methods, and the results will be greatly affected by inevitable noise. Automatic measurement of spinal parameters is the application of artificial intelligence in medicine and orthopedics, and is considered to be an significant tendency in the next few years. Breakthroughs in machine vision will contribute to the development of medical imaging. Improving diagnostic criteria for spinal diseases through "human-machine" integration will help improve medical standards and reduce medical costs.

## Surgical treatment

Artificial intelligence, especially deep learning, is promoting the development of several fields. Virtual reality (VR) and augmented reality (AR) are being expected to benefit more from advances in AI. The advantages of deep learning in object tracking and segmentation and video resolution enhancement can reduce the computing power required by AR and VR systems, reduce the cost of hardware and software, improve equipment performance and enable new functions. These abilities have significantly increased the extent of applications of AI and AR in spinal surgery, which lead to the approval of the first AR assisted spinal surgery systems by the US Food and Drug Administration in June 2020.

In spinal surgery, augmented reality AI systems have been used in pedicle screw placement (34, 35). Proper placement of pedicle screws is critical to the strength and durability of the screws. In 2017, Ma et al. (36) from Tsinghua University proposed a original AR based navigation system for pedicle screw placement. They take advantage of ultrasound to connect 3D anatomical markers to CT images, using Kirschner wire (K-wire) instead of pedicle screws, and compared their system with a skin marker tracer system. Their ultrasound AR system showed an average positioning error of 3.79 mm and an average Angle error of 4.51°, while the skin marker tracer system showed an average positioning error of 5.18 mm and an Angle error of 5.89°.

Although AR and VR still have some challenges. The bond of robot-assisted navigation systems with AR and AI can produce quick and accurate navigation systems. AI, wearable devices and AR can be integrated to provide real-time feedback to surgeons at the time of surgery. Combining AI, AR, and VR can facilitate remote instruction and its integration with wearables, while AI and surgical robots enable remote and semi-automatic surgery. Through collaboration between clinicians and engineers, we will have the ability to bring all of these fields together over the next decade to profoundly improve the way spine surgery is performed.

## Predict the prognosis

Machine learning as an emerging technology, its advantage in medical diagnosis and imaging has been well proven (37). However, it has recently been applied to epidemiological data sets to predict a variety of health-related outcome (**Table 3**). Just like simple regression models, machine learning algorithms can predict outputs given some inputs (43). However, statistical knowledge used in machine learning are more complex in generating predictions from input data. Machine learning has a lot of advantages including the capacity to process big data sets and capture nonlinear relationships compared with traditional statistical models (43). And its superiority over the traditional model has been proved in the literature (44).

In 2021, Khan et al. (38) developed a machine learning model to predict the deterioration of functional status of patients with cervical spondylotic myelopathy after surgical intervention, and identified important predictors of imaging prognosis as a potential tool for guiding surgical decision making. 757 patients were enrolled in the study. After using 8:2 train-test segmentation to the data set, they trained, optimized and tested many ML algorithms to assess algorithm

TABLE 3 AI and ML in the task of predicting the prognosis.

| Author | Models | Dataset | Type of outcome | Result |
|---|---|---|---|---|
| Khan et al. (38) | SVM | 757 patients | Change in mJOA at 1 year | AUC 0.834 |
| Karhade et al. (39) | Bayes | 1,790 patients | 30-day mortality | AUC 0.782 |
| Kuris et al. (40) | NN | 63,533 patients | 30-day readmission | AUC 0.64–0.65 |
| Karhade et al. (41) | Stochastic Gradient | 2,737 patients | Sustained postoperative opioid prescription | AUC 0.81 |
| Wang et al. (42) | ANN | 12,492 patients | Complications | AUC 0.748 |

performance and identify predictors of worse mJOA after 1 year. The highest-performing ML algorithm was a polynomial support vector machine which showed good calibration and discrimination on the testing data, with an area under the receiver operating characteristic curve of 0.834 (accuracy: 74.3%, sensitivity: 88.2%, specificity: 72.4%). Vital predictors of functional decline at 1 year included initial mJOA, male sex, duration of myelopathy, and the presence of comorbidities. The development of these algorithms provides a reference for clinicians to identify and timely manage patients at risk for further neurological deterioration after surgery. In 2018, Karhade et al. (39) assessed the efficacy of several machine learning models in predicting 30-day mortality after spinal metastasis surgery. The algorithm has the best performance in recognition, calibration and overall performance, and is integrated into an open access web application. As the volume of oncology data continues to grow, establishing learning systems and deploying them as accessible tools may greatly strengthen prediction and management. Kevin et al. (45) used a Bayesian classification algorithm to predict 30-day mortality after spinal tumor resection from the National Surgical Quality Initiative Program. The algorithm exceeds the predictive power of the National Surgical Quality Initiative mortality probability Calculator. Multivariate regression analysis showed that smoking history, chronic obstructive pulmonary disease, cancer cell spread, history of hemorrhagic disease, dyspnea, and low albumin levels were strongly associated with 30-day mortality. As the model continues to learn from input patient data, its accuracy increases. Patient outcomes can be improved by using the algorithm to identify high-risk individuals early and applying this data to preoperative decision-making as well as patient selection and education. In 2020, Nida et al. (46) from Harvard Medical School, used the American College of Surgeons National Surgical Quality Improvement Program database to develop and validate preoperative predictive variables for patients with adverse events occurring within 30 days after degenerative lumbar spondylolisthesis surgery. The predictive probabilities obtained from the best predictive models were uploaded to a publicly accessible website. It is proved that it is feasible to develop machine learning algorithms from large data sets for patient consultation and surgical risk assessment.

Readmission within 30 days of surgery can impose a heavy financial burden on clinicians and hospitals, and sometimes lead to negative outcomes for patients. Previous studies have identified risk factors for readmission, but conclusions about specific patients remain vague. Kuris et al. (40) used the American College of Surgeons National Surgical Quality Improvement Program database to developed a neural network model to predict 30-day readmission for 63,533 patients who underwent anterior, lateral, or posterior lumbar fusion surgery with area under the curve values of 0.64–0.65. Multivariate regression showed that age >65 years and American Society of Anesthesiologists(ASA) class > II were associated with increased risk for readmission for all three procedures. A study that also used the database identified that advanced age (50 years), anterior and posterior spinal fusion surgery, elevated American Society of Anesthesiologists grade, and isolated tumor diagnosis are risk factors for readmission (47). A separate analysis from national and single-institution registries showed that higher-than-average and upper quartile surgery duration and Medicare/Medicaid insurance were also related to an increased risk of readmission.

In addition to predicting functional improvements and complications after surgery, the new AI technology can also make recommendations for the medications after surgery. In 2019, Karhade et al. (41) proposed solutions for opioid abuse, particularly the continued use of opioids after spinal surgery. Although many demographic and clinical features have previously been identified as prognostic factors for continued opioid use after spinal surgery, there is currently no predictive algorithm for preoperative risk stratification of patients. The model can stratify the risk of these patients before surgery, making it possible to intervene early to reduce the likelihood of long-term opioid use.

In recent years, ACDF has become popular in ambulatory surgical Settings. There is currently no agreed risk stratification tool to identify patients who might be safe candidates for ambulatory ACDF. In 2021, Wang et al. (42) used an artificial neural network model to stratify the risk of ACDF in 12,492 patients from the National Surgical Quality Improvement Program database. Patients would be regarded as “unsafe” for outpatient surgery if they suffered any complication within a week of the index operation. The ANN showed an AUC of 0.740, which was significantly higher than

the AUCs of ASA ($P < 0.05$). Advanced age, low hemoglobin, high international normalized ratio, low albumin, and poor functional status were considered to be significant in the multivariable predictive model.

Clinicians can provide personalized treatment and counseling methods for patients by accurately predicting outcomes based on a patient's phenotype and clinical presentation. The integrated prediction in the field of degenerative disease of the spine will improve the decision of prognosis and the subsequent delivery of personalized medicine based on those prognosis. Considering the potential consequences of overestimating or underestimating the results of such studies for clinical decision making, the improper application of machine learning is a major bioethical challenge. Solutions to this problem include receiving the machine learning black box and testing. In short, we need a healthy skepticism of machine learning and a willingness to appreciate its methodology.

## Decision support systems

Decision support systems, a widely used predictive analytics application in clinical practice, utilize the predictive power of models to support clinical decision making by providing personalized predictions. In 2018, Varghese et al. (48) aimed to build a learning-based predictive model to understand the sensitivity of pedicle-screw holding power to various factors. Of the various machine-learning techniques, the random forest regression model performed well in predicting the pullout strength with a correlation coefficient of 0.99 between the observed and predicted values. The model was able to predict the holding power of a pedicle screw for any combination of density, insertion depth, and insertion angle for the chosen range. Similarly, in 2019, Khatri et al. (49) used an experimental dataset of 48 data points as training data to construct a model based on different machine learning algorithms. They also used the L9 orthogonal array of Taguchi Design of Experiments to obtain the best combination of parameters for predicting the pullout strength. Finally, random forest performed the best with a correlation coefficient of 0.96. The model developed in this study can help surgeons be better prepared for surgery and the decision would be based on objective, rather than subjective parameters.

## Future prospectives

The applications of AI technologies in healthcare, especially regarding tools with a direct clinical impact such as those aimed at clinical decisions support systems, should be in a better monitoring environment for ethical reasons. The use of AI in healthcare also raises serious concerns about data privacy and security due to the massive amount of clinical and imaging data required for training and validation of the tools. In the future, we should pay more attention to data security to ease people's concerns about privacy disclosure.

## Summary

At present, the application of artificial intelligence in spine surgery is still in its infancy stage, facing many challenges, such as scattered data, integration degree is not enough, and clinical conversion efficiency is low. Better integration, mining and management of unstructured data will contribute to the further development of artificial intelligence in spine surgery. In the future, the application of artificial intelligence and machine learning technology in spinal surgery will be conducive to improving the level of medical diagnosis and treatment, optimizing the medical process, developing the clinically assisted decision-making system, and alleviating the pain of patients and reducing the social and economic burden.

## Author contributions

SZ conceptualized the study, retrieved, read, and summarized the articles, and wrote the manuscript. YS, XC, YD, YZ, HH, XF, GZ, and XL retrieved and summarized the articles and wrote the manuscript. FZ reviewed and edited the manuscript and supervised the review and writing process. All authors contributed to the article and approved the submitted version.

## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2022.885599/full#supplementary-material.

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# Risk factors for contralateral hip refractures in patients aged over 80 years with intertrochanteric femoral fractures

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**Purpose:** The purpose of this study was to identify which of the risk factors would contribute to the contralateral fracture in very elderly patients after intramedullary nail fixation.
**Methods:** Clinical data of 227 intertrochanteric fracture patients aged 80 years or older were retrospectively reviewed. Intramedullary nails (IMNs) were used on all of the patients. Potential risk factors for contralateral hip refractures were determined using univariate and logistic regression analyses.
**Results:** Contralateral hip refractures occurred in 11 patients (4.84%). Univariate analysis revealed that age, gender, body mass index, fracture classification, hematocrit, D-dimer, and CRP level were not associated with contralateral fractures ($P > 0.05$). However, neurological diseases, cardiovascular disease, and visual impairments were significantly associated with contralateral fractures ($P < 0.05$). Multivariate analysis further revealed that neurological diseases (OR 4.25, $P = 0.044$) and visual impairments (OR 5.42, $P = 0.015$) were independent risk factors associated with contralateral refractures.
**Conclusion:** To prevent contralateral refractures, more attention should be paid to elderly intertrochanteric fracture patients with underlying neurological disease and visual impairments.

KEYWORDS
contralateral hip refracture, intertrochanteric fracture, intramedullary nails, elderly patients, refractures

## Introduction

Hip fractures remain a worldwide epidemic and costly injury in the elderly, and the number of patients will increase significantly in the future (1, 2). Some investigational data have shown that between 1.2% and 9% of patients who have a hip fracture will suffer a contralateral refracture within 1 year (3, 4) and up to 20% in the course of their lives (5–7). Second contralateral fractures are related to significantly higher complication rates, socioeconomic cost, and mortality than the first fractures (8–11).

Associations between several risk factors and contralateral fractures have been reported, including gender, osteoporosis, body mass index (BMI), dementia, diabetes, and heart disease (12, 13). In general, patients aged over 80 years are

more susceptible to medical comorbidities and possibly at high risk of contralateral fracture (14, 15). Another characteristic of elderly patients is that advanced age is more strongly associated with the risk of intertrochanteric fractures than femoral neck fractures, and intramedullary nails (IMNs) are recommended for fixation (16–18). Some studies, for example, on femoral neck fractures, have revealed that specific fixation methods are associated with a different risk of second hip fracture (19–22). One possible explanation is that surgical fixation may alter an individual's gait and subsequently increase the fall risk by changing muscle moment and bone structure at the fracture site (23). Similarly, for intertrochanteric fractures, intramedullary nailing has been shown to alter the strength of hip muscles and the walking gait (24, 25). However, no research has been able to determine the IMN relative risk for contralateral refractures, especially in patients of advanced age. We hypothesized that the incidence and risk factors of these patients might differ from those of the general population. The aim is to explore potential contralateral fracture risk factors for intertrochanteric fracture patients who aged over 80 years and were treated with intramedullary nails.

# Materials and methods

Medical records of 227 eligible patients who had been treated for intertrochanteric fracture in our institution from January 2019 to January 2021 were retrospectively reviewed. In the study, intertrochanteric fractures were classified using AO/OTA criteria (26, 27). The inclusion criteria are as follows: (1) ≥80 years old; (2) intertrochanteric fractures; and (3) stabilized with proximal femur nail antirotation (PFNA). Patients with the following conditions were excluded: (1) hip fractures caused by high-energy trauma; (2) open fractures; (3) pathological fractures caused by bone tumors; and (4) incomplete clinical information. The involvers were monitored until a contralateral hip fracture occurred until February 2022. The study was reviewed and approved by the Ethics Committee of our institution.

Various parameters were analyzed to identify potential risk factors for contralateral refractures. The following clinical information is carefully extracted from their clinical data: age, gender, body height/weight, BMI, living circumstances, fracture site, and classification. Comorbidities are categorized as follows: hypertension, cardiovascular disease, diabetes mellitus, respiratory disease, neurological diseases, and visual impairments. The category of cardiovascular disease included coronary atherosclerotic heart disease, cardiomyopathy, heart failure, and arrhythmia. Respiratory diseases included bronchiectasis, pulmonary tuberculosis, chronic obstructive obstructive pulmonary disease (COPD), chronic bronchitis, and bronchial asthma. The category of neurological diseases included dementia, Parkinson's disease, intracerebral hemorrhage, and stroke. Cataract, diabetic retinopathy, retinal neurodegeneration, and glaucoma are all examples of visual impairments. Surgical information included time from fracture to surgery, operation time, and intraoperative blood loss (ml). Peripheral blood samples were collected for laboratory tests including hematocrit (HCT), hemoglobin levels, D-dimer, and C-reactive protein (CRP).

## Statistical analysis

Continuous data were presented as mean ± standard; categorical data were expressed as frequencies. Statistical analyses were performed using Student's $t$-test or $\chi^2$ test relatively. Multivariate analysis was performed using logistic regression analysis to determine the risk factors, and results were presented as the odds ratios (OR) by 95% confidence interval (CI). $P < 0.05$ was considered statistically significant.

# Results

The general clinical features of the two groups are presented in Table 1. A total of 234 patients were enrolled in the study; 7 patients were excluded due to a lack of data on whether a contralateral hip fracture occurred. A total of 227 individuals were finally included, including 75 males and 152 females. Contralateral hip refractures occurred in 11 patients (4.84%) within 1 year after the surgery, including 1 male patient and 10 female patients. Each of the 11 patients had a history of falling and sustaining an injury.

The baseline data from the two groups were compared. No significant differences were found in age, gender, BMI, fracture site, AO/OTA classification, time from fracture to surgery, operation time, and intraoperative blood loss between the contralateral fracture and nonfractured patients ($P > 0.05$).

There was no significant statistical difference between the 11 patients and the 216 controls when preoperative and postoperative laboratory tests of hematocrit, D-dimer level, and C-reactive protein level were examined ($P > 0.05$; Table 2). In addition, no statistical difference was founded in hemoglobin levels between the contralateral fracture and nonfractured patients ($P > 0.05$).

For comorbid medical diseases, contralateral fracture patients had higher rates of hypertension, cardiovascular disease, neurological diseases, respiratory disease, and visual impairments than the control group (Table 3). However, only visual impairments and neurological and cardiovascular diseases were seen as significantly different between the two groups ($P < 0.05$).

Univariate analysis revealed that demographic characteristics, fracture features, and laboratory tests were not

TABLE 1 Comparison of baseline data between the two groups.

| Characteristics | Non-refractured ($n = 216$) | Refractured ($n = 11$) | $t/\chi^2$ value | $P$-value |
|---|---|---|---|---|
| Age, years (SD) | 83.63 ± 3.25 | 83.27 ± 2.83 | 0.440 | 0.725 |
| Gender (male/female) | 74/142 | 1/10 | | 0.106 |
| Body height (cm) | 163.3 (7.49) | 162.4 (8.64) | 0.422 | 0.674 |
| Body weight (kg) | 63.74 | 66.27 | 0.668 | 0.505 |
| Body mass index (kg/m$^2$) | 23.80 ± 3.76 | 25.07 ± 3.82 | 1.085 | 0.279 |
| Living circumstances | | | | |
| Assisted living | 216 (100%) | 11 (100%) | | >0.999 |
| Other | 0 | 0 | | |
| Fracture site | | | | 0.117 |
| Right | 101 (46.76%) | 2 (18.18%) | | |
| Left | 115 (53.24%) | 9 (81.82%) | | |
| AO/OTA classification | | | | 0.665 |
| A1.1–A1.3 | 54 (25.00%) | 2 (18.18%) | | |
| A2.1–A2.3 | 140 (64.81%) | 7 (63.64%) | | |
| A3.1–A3.3 | 22 (10.19%) | 2 (18.18%) | | |
| Time from fracture to surgery (days) | 4.54 ± 3.04 | 5.27 ± 2.97 | 0.783 | 0.434 |
| Operation time (min) | 90.69 ± 28.27 | 87.27 ± 36.63 | 0.386 | 0.700 |
| Intraoperative blood loss (ml) | 283.02 ± 155.06 | 277.2 ± 108.08 | 0.121 | 0.904 |

TABLE 2 Comparison of laboratory tests between the two groups.

| Characteristics | Nonrefractured ($n = 216$) | Refractured ($n = 11$) | $t$ value | $P$-value |
|---|---|---|---|---|
| Hematocrit | | | | |
| Preoperation | 0.34 ± 0.05 | 0.33 ± 0.04 | 0.832 | 0.406 |
| Postoperation | 0.34 ± 0.07 | 0.31 ± 0.04 | 1.494 | 0.137 |
| Hemoglobin levels | 118.32 ± 17.48 | 110.36 ± 14.59 | 1.483 | 0.139 |
| D-dimer | | | | |
| Preoperation | 1207.77 ± 1350.00 | 1227.27 ± 925.30 | 0.0473 | 0.962 |
| Postoperation | 677.26 ± 567.22 | 581.82 ± 315.65 | 0.553 | 0.581 |
| C-reactive protein | | | | |
| Preoperation | 39.15 ± 36.70 | 43.36 ± 49.10 | 0.365 | 0.716 |
| Postoperation | 54.59 ± 38.57 | 65.82 ± 42.73 | 0.937 | 0.350 |

TABLE 3 Comparison of comorbidity between the two groups.

| | Nonrefractured ($n = 216$) | Refractured ($n = 11$) | $P$-value |
|---|---|---|---|
| Hypertension | 117 (54.17%) | 8 (72.73%) | 0.353 |
| Cardiovascular disease | 49 (22.69%) | 6 (54.55%) | 0.026 |
| Diabetes mellitus | 58 (26.85%) | 2 (18.18%) | 0.732 |
| Respiratory diseases | 26 (12.04%) | 3 (27.27%) | 0.153 |
| Neurological diseases | 36 (16.67%) | 5 (45.45%) | 0.030 |
| Visual impairments | 32 (14.81%) | 5 (45.45%) | 0.019 |

TABLE 4 Univariate and multivariate analyses of factors.

| | OR | 95% CI | $P$-value |
|---|---|---|---|
| Cardiovascular disease | 2.53 | 0.63–9.98 | 0.177 |
| Neurological diseases | 4.25 | 1.02–18.17 | 0.044 |
| Visual impairments | 5.42 | 1.35–22.16 | 0.015 |

associated with contralateral fractures. However, neurological diseases, cardiovascular disease, and visual impairments were significantly associated with contralateral fractures. Multivariate analysis further revealed that visual impairments (OR 5.42, $P = 0.015$) and neurological diseases (OR 4.25, $P = 0.044$) were independent risk factors for contralateral hip refractures (Table 4).

## Discussion

Contralateral hip refractures are associated with major clinical and social cost implications (4, 11, 28, 29). How to develop effective preventive strategies for hip fracture patients is still under controversy (13). Recently, reports have raised the question of whether specific surgical fixation of the initial hip fracture is associated with a different risk of subsequent contralateral fracture. Souder et al. (22) found an increased risk of hip refractures in patients who underwent closed reduction and percutaneous puncture compared to those who underwent arthroplasty. Changes in individual's gait and subsequent fall risk due to different fixation methods may be

one of the important reasons (23, 24). To our knowledge, no research has determined the IMN relative risk of contralateral hip refractures, especially in patients of advanced age.

Our results showed that 11 in 227 patients (4.84%) suffered a contralateral hip refracture during the data collection period. The incidence correlated with the risk of 3%–10% for second hip refractures (3, 20, 30, 31). In general, elderly patients are prone to contralateral fractures due to osteoporosis and susceptible to medical comorbidities (15). However, only a few studies have reported the age-specific incidence and risk factors for contralateral fractures. Yamanashi et al. (32) reported that the incidence was 3.8% within the first year in patients aged ≥65 years. Similarly, Lönnroos et al. (33) noted an incidence of 5.08% for patients aged ≥60 years within the first year, and the rate increased further to 8.11% at 2 years following the initial fracture. For very elderly patients, Vochteloo et al. (34) found that the incidence of patients aged over 85 years was not different from other age categories. Lawrence et al. (35) also found female patients over the age of 84 years have a similar risk to the general population. Similarly, our results showed that the incidence of patients aged over 80 years was not significantly increased compared to previous hip refracture data. One theoretical explanation is that the increasing age of patients is not exclusively related to bone strength loss. Indeed, Gnudi et al. (36) suggested that bone loss will gradually slow down after the age of 65 years. Moreover, we noted that none of the enrolled patients lived alone and had a reduced range of physical activity, which may have reduced the risk of falls, which are a major cause of hip fractures.

To further identify risk factors, we evaluated the difference between the patients who suffered a contralateral hip fracture and those in the control group. Univariate analysis revealed that gender distribution, BMI, fracture classification, operation time, and intraoperative blood loss were not associated with contralateral fractures. Although some authors have emphasized the relationship between gender and second hip fractures (7, 31), our study did not support this suggestion. Similar to our results, no significant gender difference was also seen in previous studies (15, 33, 34, 37, 38).

At present, few publications have emphasized the value of laboratory-based indicators for contralateral fracture risk. Preoperative CRP was found to be a primary risk factor for postoperative death in elderly patients with hip fractures in a recent study (39). Chen et al. (37) reported that the serum CRP/Alb ratio is a risk factor in elderly hip fracture patients treated by total hip arthroplasty. In our study, there was no difference between the patient's preoperative and postoperative laboratory tests of hematocrit, D-dimer level, and CRP level between the two groups. Traumatic stress and perioperative drugs all affect the level of expression of these inflammatory and nutritional indicators in the perioperative period (40); therefore, their significance in contralateral fracture needs to be further evaluated.

An increased risk of contralateral hip refractures has been found to be associated with several comorbid diseases (12, 13, 38, 41–43), including hypertension, diabetes mellitus, cardiovascular disease, neurological diseases, respiratory diseases, and visual impairments. In our study, neurological diseases and visual impairments were found to be significantly associated with contralateral hip refractures. Although contralateral fracture patients had higher rates of hypertension, cardiovascular disease, and respiratory diseases than the control group, differences were only seen in neurological diseases, cardiovascular disease, and visual impairments using univariate analysis. Multivariate analysis revealed that neurological diseases and visual impairments were independent risk factors for contralateral hip refractures. Risk factors determined in our study can aid in identifying high-risk populations among very elderly intertrochanteric fracture patients. However, our research also has some limitations. Some clinical information was collected retrospectively, and a relatively small population was the study's main limitation. This may have led to a bias in the analysis of the incidence of contralateral fractures. In addition, some potentially meaningful items, such as the clinical data on vitamin D levels and the use of bone health medications (vitamin D, bisphosphonates, trospium) were not available for all patients, so this was not analyzed in the study.

In summary, neurological diseases and underlying visual impairments are risk factors for contralateral hip refractures in intertrochanteric fracture patients aged over 80 years and who were treated with intramedullary nails. More attention should be given to the patients with these underlying comorbidities.

## Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author/s.

## Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of Tianjin Hospital. The patients/participants provided their written informed consent to participate in this study.

## Author contributions

SY and SW designed the study. CL, YZ, and JZ collected clinical data and performed statistical analysis. ZZ and SW

wrote the manuscript. SY and YZ revised the manuscript. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



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# Arthroscopic therapy of rotator cuff diseases: A bibliometric study of the past 2 decades (2002–2021)

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**Purpose:** Rotator cuff diseases, as a common cause of shoulder pain and disability, have seriously affected the patients' daily life. Rotator cuff repair techniques have been a hot topic in the arthroscopic therapy field. Our study was to use bibliometrics analysis to clarify the current status and research trends in the field of arthroscopic therapy of rotator cuff diseases.
**Methods:** The publications relating to arthroscopic therapy of rotator cuff diseases published from 2001 to 2021 were obtained from the Web of Science Core Collection (WoSCC) database. The R software and VOSviewer software were used for the cross-sectional bibliometric and scientometric analysis.
**Results:** A total of 4,567 publications about arthroscopic therapy of rotator cuff diseases published between 2002 and 2021 retrieved from the WoSCC database were analyzed in our study. The results showed that the United States made the largest contribution to this field. The most relevant institutions were Seoul National University, Rush University, and Hospital for Special Surgery. Stephen S Burkhart was the most relevant researcher in this field with the largest number of publications, as well as the highest H-index and G-index. The journal ARTHROSCOPY contributed the largest number of publications in the past 2 decades. Considering the H-index and G-index, ARTHROSCOPY was also the journal with the largest impact in this field.
**Conclusions:** Arthroscopic Therapy of Rotator Cuff Diseases Related research presented a rising trend in the past 2 decades. The United States can be regarded as the leader because of its huge contributions to this field. The journal ARTHROSCOPY published the largest number of publications in this field. It can be predicted that research about advanced arthroscopic techniques and postoperative pain management of patients with rotator cuff diseases will be the next research hotspots in the following years.

KEYWORDS

arthroscopy, arthroscopic therapy, rotator cuff diseases, bibliometric analysis, web of science

# Introduction

The rotator cuff, a network structure composed of ligaments, tendons, and other connective tissues, provides stability and extremely high flexibility for the shoulder (1). However, these tissues can be injured or degenerate due to various mechanisms, including traumatic incidents, long-term repetitive activities, age-related degenerative changes of the tendon, and so on (2). Rotator cuff diseases are a common cause of shoulder pain and disability causing decreased performance in daily activities (3). Studies showed that age was a significant risk factor for rotator cuff diseases. Aging can change the physiologic characteristics and biomechanical properties of the tendon, which may result in delayed healing and an increased risk of injuries (4). Age can be considered one of the key factors in the occurrence and severity of rotator cuff diseases (5). Rotator cuff diseases are extremely prevalent among the aging population with an incidence of 30% in patients over 60 years old and 62% in those over 80 years old (6, 7). Pain and poor performance in the range of motion (ROM) of the shoulder are the main complaints from patients. With the proportion of the aging population rapidly increasing, more and more patients are suffering from rotator cuff diseases, which not only affect daily activities and work, but sports are also greatly affected. Rotator cuff pathology undergoes a progressive process, beginning with tendon impingement in the subacromial space, progressing to partial tears, full layer tears, and even cuff tear arthropathy (CTA) (8).

Interest in the field of rotator cuff diseases has constantly increased among orthopedic surgeons and researchers recently. Various rotator cuff repair treatments have been developed from physical therapy to surgical repair. The choice of rotator cuff repair is not only based on the extent of the disease and patients' symptoms, but also the thickness, size, and morphology of the torn rotator cuff (8). Arthroscopy, as a minimally invasive orthopedic technique, is regarded as the future development trend of modern orthopedic surgery, which has been widely used in orthopedic surgery from knee diseases to other joints such as shoulder, elbow, hip, and even smaller (9). Rockwood et al. firstly performed debridement with subacromial decompression by arthroscopy for treating Rotator cuff diseases in 1995 (10). With the development of arthroscopy techniques, nowadays various arthroscopic therapy techniques have been applied in rotator cuff repair.

Bibliometric analysis is a method to clarify the current status and research trends in a specific field and identify the most valuable literature. The publications about arthroscopic therapy of rotator cuff diseases have grown annually over the past 20 years. However, no authors have conducted a comprehensive bibliometric analysis of related publications in this field in the past few years. This study aims to provide researchers with the current status and development trends of arthroscopic therapy of rotator cuff diseases research through bibliometric analysis, to identify the most valuable publications, influential journals, major researchers, and core countries in the field.

# Methods

## Database source

The cross-sectional bibliometric and scientometric analysis was conducted on February 10, 2022. The publications for arthroscopic therapy of rotator cuff diseases published from 2002 to 2021 were retrieved from the Web of Science Core Collection (WoSCC) database. WoSCC contains a worldwide variety of authoritative and high-impact academic journals covering the fields of natural sciences, engineering technology, biomedicine, social sciences, arts, and humanities. WoSCC also includes the references cited in the publications, which are indexed according to the cited author, source, and publication date. All these characteristics of WoSCC can meet the requirements for bibliometric analysis of Arthroscopic Therapy of Rotator Cuff Diseases-Related research.

## Search strategy

We adjusted the literature published timespan from 2002 to 2021. The search terms related to rotator cuff diseases were "Rotator Cuff Disease", "Rotator Cuff Disorder", or "Rotator Cuff Tear". And the search term related to arthroscopic therapy was "Arthroscopy", "Arthroscopic Treatment", or "Arthroscopic Therapy". To find all the relevant publications, we used "[Rotator Cuff (Topic)] and [Arthroscopy or Arthroscopic (Topic)]" to search the literature in the WoSCC, covering all types of studies, such as Articles, Reviews, Clinical Trials, Case Reports, Editorial Materials, Case Reports, Letters, and so on. And the title, authors, countries, institutions, abstract, keywords, and references were extracted from the WoSCC, which forms raw data for our bibliometric analysis (**Figure 1**).

## Data analysis

The "bibliometrix" package (version 3.0.3) installed in R software (version 4.1.0) provides a web interface for comprehensive science mapping analysis (11). Microsoft Excel was used to draw the line, bar, and pie charts. Citespace (version 6.1.R2) software was used for keyword burst Analysis. And the VOSviewer (version 1.6.16) software was mainly used to conduct co-occurrence, co-citation, and co-authorship analysis (12).

## Statistical analysis

In this study, a linear regression model was established for the year and the number of publications by IBM SPSS Statistics (Version R26.0.0.0), and the $P$ was set at 0.05. Most analysis results are presented in quantity and percentage ($n$, %).

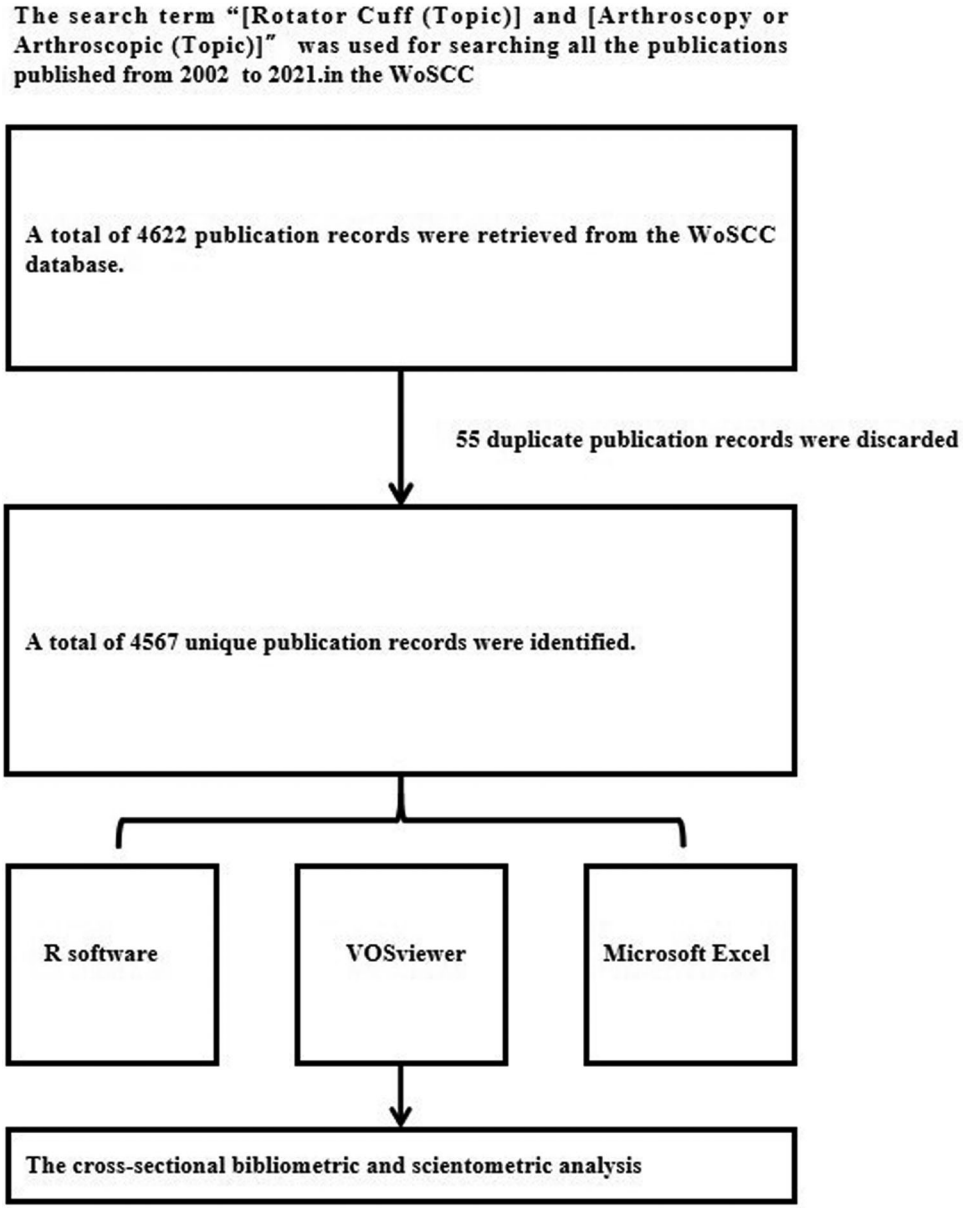



FIGURE 1
The flow chart for the "Search Strategy": a total of 4,567 unique publication records were identified for the cross-sectional bibliometric and scientometric analysis.

# Results

## General information about arthroscopic therapy of rotator cuff diseases related publications

Using the topic terms "Rotator Cuff and (Arthroscopic or Arthroscopy)", there were a total of 4,622 records found in the WoSCC database. And 55 duplicate and incomplete records were removed. Finally, there were 4,567 document records (Article, 3,848, 84%; Review, 501, 11%; Editorial Material, 173, 4%; Letter, 45, 1%) published between 2002 and 2021 retrieved from the WoSCC database analyzed in this bibliometric analysis (Figure 2A). All of these document records were from 437 sources (Journals, Books, etc.). There were 11,559 authors and 66 countries contributing to this field. The number of publications relating to arthroscopic therapy of rotator cuff diseases showed a rising growth trend from 64 in 2002 to 471 in 2021 (Figure 2B). The 95% confidence interval (CI) of the number of publications in 2022 predicted by the linear regression model is (377,573) ($P < 0.05$) (Figure 2).

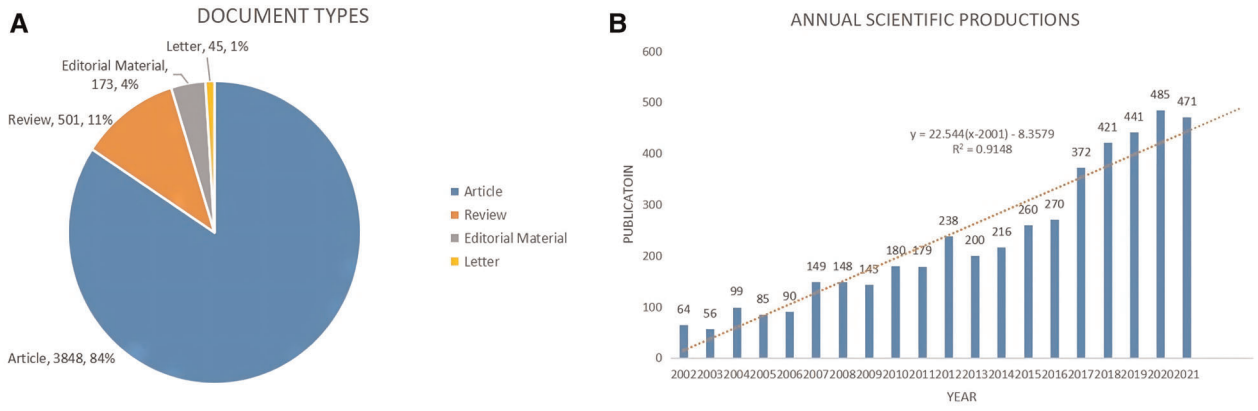



FIGURE 2
General information about arthroscopic therapy of rotator cuff diseases related publications from 2002 to 2021. (A) The document types of Arthroscopic Therapy of Rotator Cuff Diseases Related Publications. (B) The annual scientific productions of Arthroscopic Therapy of Rotator Cuff Diseases Related Publications.

## Country and institution analysis

The characteristics of the countries and institutions of the document records were analyzed by the bibliometrix package (version 3.0.3) running in R software (version 4.1.0). 95 countries contributed to Arthroscopic Therapy of Rotator Cuff Diseases-Related publications. As Figure 3A showed, the largest number of publications was contributed by the United States (35%), followed by South Korea (9%), Germany (6%), China (5%), France (5%), Canada (5%), and Italy (4%). The national contribution map produced by the data visualization technology showed that North America, Europe, East Asia, and Oceania were the main research areas (Figure 3B: gray indicates a small number of productions, blue indicates a large number of productions, and the depth of the color increases with the number of productions).

Citation analysis can be used to identify the impact of articles, countries, or authors in specific fields. Based on the document records retrieved from the WoSCC database, Arthroscopic Therapy of Rotator Cuff Diseases-Related publications from the United States possessed the highest total citation frequencies (48,508 times), followed by Korea (9,219 times), France (5,376), the UK (4,969 times), and Germany (4,778 times). In the terms of average citation frequencies per document, the top five countries were South Africa (39 times), Norway (37.95 times), Luxembourg (37.667 times), New Zealand (31.286 times), and France (29.702 times) (Figure 3C).

There are a total of 3,254 institutions contributing to Arthroscopic Therapy of Rotator Cuff Diseases-Related research between 2002 and 2021. Seoul National University ranked first with 144 publications, followed by Rush University (141 publications), Hospital for Special Surgery (110 publications), Washington University (99 publications), and Sungkyunkwan University (94 publications). Among the top 30 relevant affiliations, there were 16 located in the United States, 8 located in Korea, 2 located in Canada, 1 located in the UK, 1 located in Germany, 1 located in Italy, and 1 located in Switzerland (Figure 3D).

## Author analysis

A total of 11,559 researchers were involved in Arthroscopic Therapy of Rotator Cuff Diseases-Related research. The author who participated in the largest number of publications was Stephen S Burkhart (San Antonio Orthopaedic Group, Burkhart Research Institute for Orthopaedics) with 88 publications, followed by Peter J Millett (Steadman-Philippon Research Institute; Steadman Clinic) with 73 publications, Anthony A Romeo (Rothman Institute Department of Orthopaedic Surgery) with 72 publications, and Nikhil N Verma (Rush University Medical Center) with 68 publications, and Sae Hoon Kim (Department of Orthopedic Surgery, Seoul National University Hospital, Seoul National University College of Medicine) with 63 publications (Figure 4A). Figure 4B showed the top 5 authors' production over time. Stephen S Burkhart had a high publication output during 2003–2007 and 2010–2012. Peter J Millett entered a period of high output after 2014. Anthony A Romeo, Nikhil N Verma, and Sae Hoon Kim output productions in a stable manner.

The H-index can be used to evaluate the number of academic outputs and the level of academic outputs of researchers, which can reflect the author's impact in a specific field. In terms of the H-index, the top 5 authors were Stephen

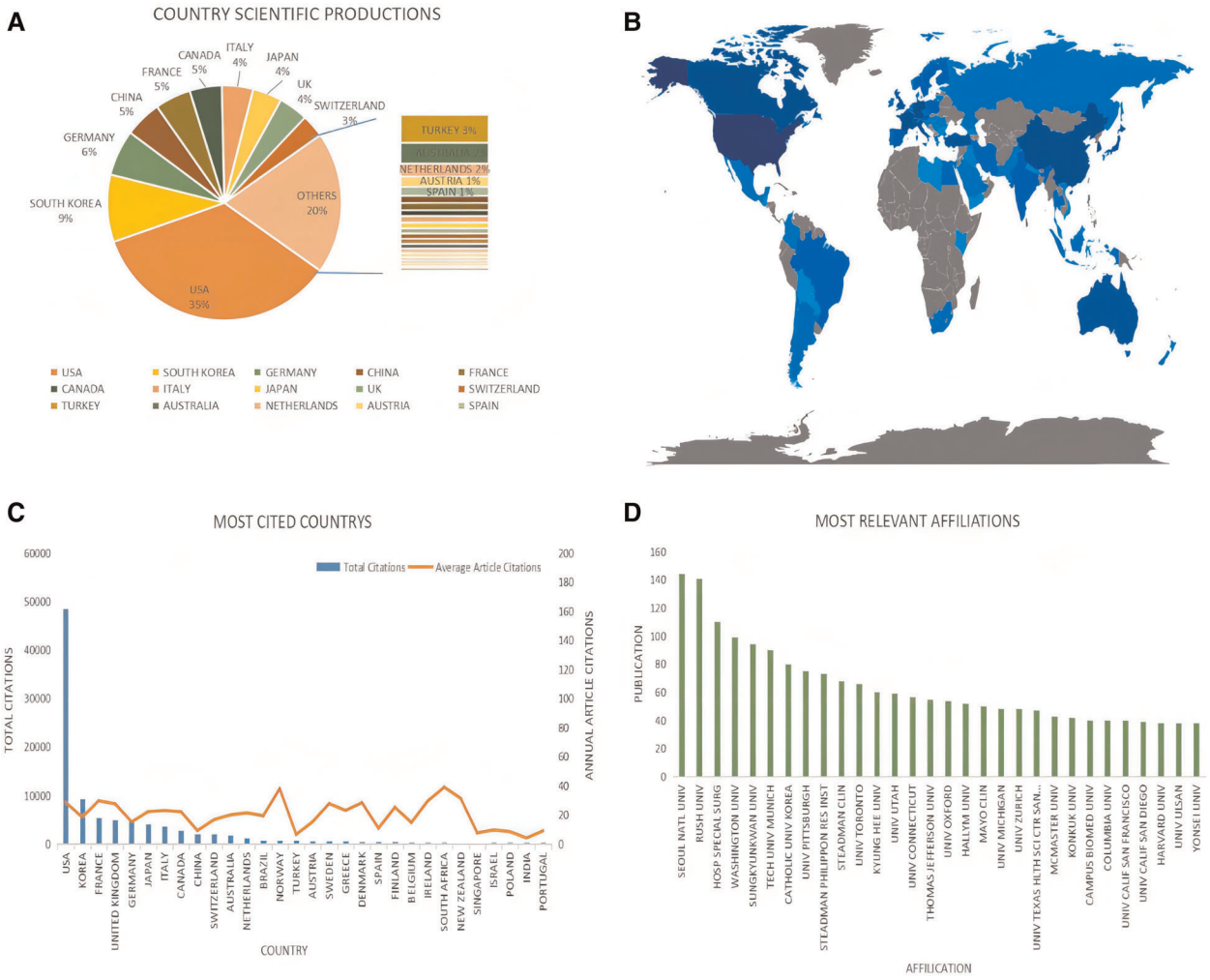



FIGURE 3
Country and institution analysis of arthroscopic therapy of rotator cuff diseases related publications from 2002 to 2021. (A) The production proportion of contributing countries. (B) Heat Map of the country's scientific productions. (C) The total citations and annual article citations of the top 50 countries. (D) The number of publications of the top 30 most relevant countries.

S Burkhart with an H-index of 42, Anthony A Romeo with an H-index of 28, Sae Hoon Kim with an H-index of 26, Nicola Maffulli (Department of Medicine, Surgery and Dentistry, University of Salerno; School of Pharmacy and Bioengineering, Keele University Faculty of Medicine; Barts and the London School of Medicine and Dentistry, Centre for Sports and Exercise Medicine, Mile End Hospital) with an H-index of 25, and Nikhil N Verma with an H-index of 25. The G-index is a derivative of the H-index, which can also be used to reflect the impact of the authors. Generally speaking, $G \geq H$ and the higher the number of citations, the higher the G-index. Stephen S Burkhart also ranked first with the highest G-index of 65, followed by Nicola Maffulli with a G-index of 48, Anthony A Romeo with a G-index of 45, Sae Hoon Kim with a G-index of 45, and Vincenzo Denaro (Department of Orthopaedic and Trauma Surgery, Campus Bio-Medico University) with a G-index of 45 (Figure 4C).

## Journal analysis

437 Journals published Arthroscopic Therapy of Rotator Cuff Diseases-Related publications. ARTHROSCOPY ranked first, which contributed the largest number of publications with 773 papers in the past 2 decades, followed by JOURNAL OF SHOULDER AND ELBOW SURGERY with 532 papers, AMERICAN JOURNAL OF SPORTS MEDICINE with 414 papers, KNEE SURGERY, SPORTS TRAUMATOLOGY, ARTHROSCOPY with 239 papers, and ARTHROSCOPY TECHNIQUES with 141 papers (Figure 5A). Based on the

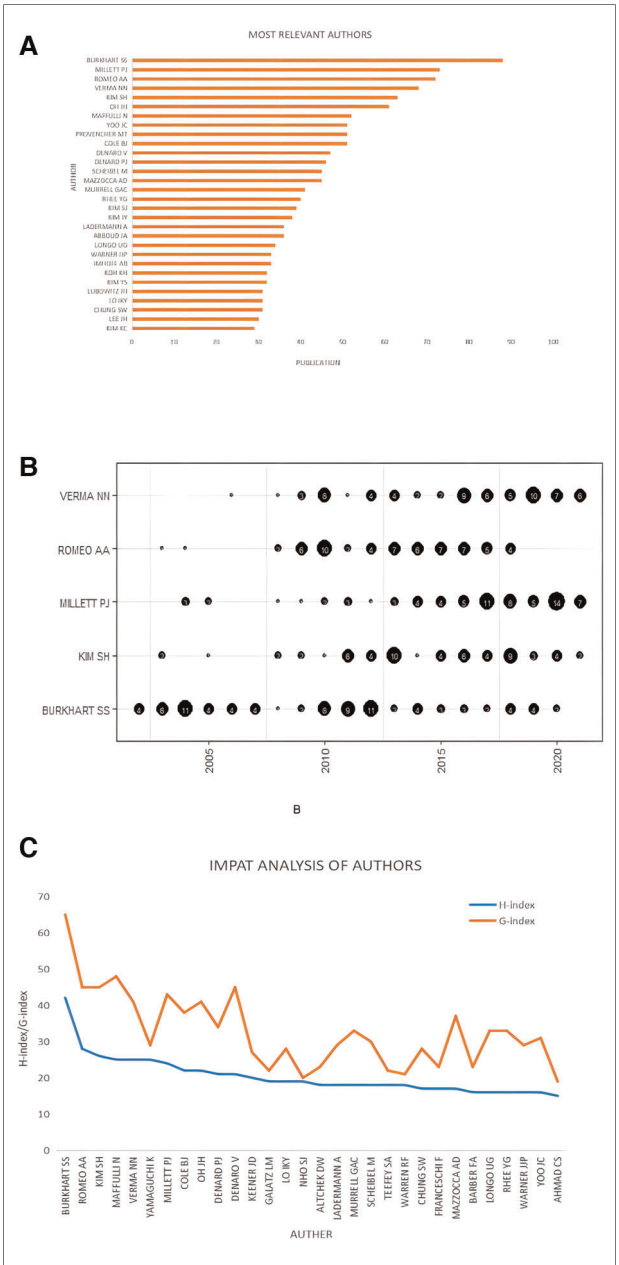



FIGURE 4
Author analysis of arthroscopic therapy of rotator cuff diseases related publications from 2002 to 2021. (A) The number of publications of the top 30 most relevant authors. (B) The analysis of the top 5 most relevant authors' production over time. (C) The H-index and G-index of the top 30 most relevant authors.

analysis of references records, the top 5 highly cited journals were ARTHROSCOPY (24,917 times), JOURNAL OF SHOULDER AND ELBOW SURGERY (18,465 times), JOURNAL OF BONE AND JOINT SURGERY-AMERICAN VOLUME (17,748 times), AMERICAN JOURNAL OF SPORTS MEDICINE (16,978 times), and CLINICAL ORTHOPAEDICS AND RELATED RESEARCH (7,575 times) (Figure 5B).

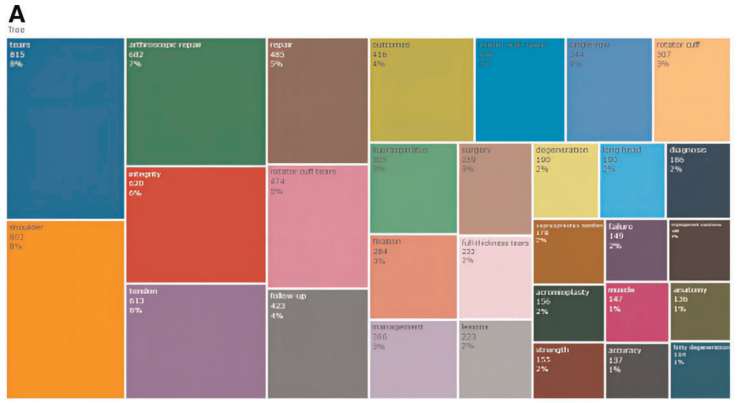
The H-index and G-index of journals can reflect the impact of journals in a certain field. H-index, also called H-factor, implies that the n of papers with at least n citations. G-Index can be regarded as an improvement on the H-index, which is used to make up for the deficiency of the H-index that place a low value on highly cited publications. Figure 5C showed that ARTHROSCOPY ranked first with the highest H-index of 79, followed by AMERICAN JOURNAL OF SPORTS MEDICINE with an H-index of 72, JOURNAL OF SHOULDER AND ELBOW SURGERY with an H-index of 58, JOURNAL OF BONE AND JOINT SURGERY-AMERICAN VOLUME with an H-index of 57, KNEE SURGERY, SPORTS TRAUMATOLOGY, ARTHROSCOPY with an H-index of 32. The ranking order of journals based on the G-index was consistent with H-index, except that the JOURNAL OF BONE AND JOINT SURGERY-AMERICAN VOLUME surpassed the one in front with a high H-index of 107. Figures 5D,E presented that ARTHROSCOPY, AMERICAN JOURNAL OF SPORTS MEDICINE, and JOURNAL OF SHOULDER AND ELBOW SURGERY maintained an advantage compared with other journals in the Arthroscopic Therapy of Rotator Cuff Diseases-Related field in the past 2 decades. ARTHROSCOPY TECHNIQUES showed a rapid growth trend in this field since 2016 (Figure 5).

## Keywords analysis

Keywords refer to the words that can embody the central concept of an article or a publication. By analyzing the keywords retrieved from document records, we can see the high-frequency used words in a specific period, helping to insight research trends in related fields and the emergence of new hotspots. The top 10 most frequent keywords were Tear (815 times), Shoulder (802 times), Arthroscopic Repair (682 times), Integrity (620 times), Tendon (613 times), Repair (485 times), Rotator Cuff Tears (474 times), Follow-up (423 times), Outcomes (416 times), Rotator Cuff Repair (358 times) (Figure 6A). The dynamic growth of the frequency of keywords can help us to identify the burst keywords. Figure 6B showed that the keyword "Arthroscopic Repair" became hot after 2010. There was a higher frequency of the keyword "Platelet-Rich-Plasma" since 2011. The keyword "Meta-Analysis" first appeared in the field in 2014 and then began to maintain relatively steady growth. The frequency of "Sigle-Row" is higher than that of "double-row" each year. The keyword "Muscle Atrophy", and "Fatty Degeneration" currencies in high frequency in recent 5 years.

The keyword co-occurrence analysis was conducted by Vosviewer. The cluster map of the keywords subnetwork was shown in Figure 6C. There were a total of 6 clusters identified. The biggest cluster contains 136 items, including "Shoulder", "Rotator cuff tear", "Lesions", "Anatomy",


FIGURE 5
Journal analysis of arthroscopic therapy of rotator cuff diseases related publications from 2002 to 2021. (**A**) The number of publications of the top 30 most relevant journals. (**B**) The total cited times of the top 30 most relevant journals (Analysis based on the list of references). (**C**) The H-index and G-index of the top 30 most relevant journals. (**D**) The dynamic growth of top 10 journals (Analysis based on the cumulated occurrences). (**E**) The dynamic growth of top 10 journals (Analysis based on the annual occurrences).




B

Top 46 keywords with the strongest citation bursts

| Keywords | Year | Strength | Begin | End | 2000–2018 |
|---|---|---|---|---|---|
| Follow up | 2000 | 9.2726 | 2000 | 2004 | |
| Randomized clinical trial | 2000 | 4.0606 | 2000 | 2009 | |
| Cochrane collaboration | 2000 | 3.3817 | 2000 | 2001 | |
| Health care | 2000 | 3.7539 | 2002 | 2009 | |
| Systematic review | 2000 | 6.4234 | 2003 | 2008 | |
| Clinical trial | 2000 | 5.9369 | 2003 | 2007 | |
| 1 year follow up | 2000 | 3.8326 | 2004 | 2005 | |
| Adolescent | 2000 | 3.0671 | 2004 | 2011 | |
| Manipulation | 2000 | 3.0280 | 2005 | 2008 | |
| Placebo controlled trial | 2000 | 5.5386 | 2005 | 2008 | |
| General practice | 2000 | 4.6972 | 2006 | 2010 | |
| Exercise therapy | 2000 | 3.0715 | 2006 | 2009 | |
| Acupuncture | 2000 | 3.1573 | 2007 | 2008 | |
| Guideline | 2000 | 3.0718 | 2007 | 2008 | |
| Schoolchildren | 2000 | 3.2323 | 2007 | 2011 | |
| Therapy | 2000 | 3.3109 | 2008 | 2009 | |
| Prognostic factor | 2000 | 3.3279 | 2008 | 2010 | |
| Fear avoidance belief | 2000 | 6.1676 | 2008 | 2012 | |
| Rehabilitation | 2000 | 3.3034 | 2009 | 2012 | |
| Spinal manipulation | 2000 | 4.8269 | 2009 | 2010 | |
| Sick leave | 2000 | 3.6664 | 2009 | 2012 | |
| Program | 2000 | 5.6371 | 2010 | 2013 | |
| Predictor | 2000 | 3.5190 | 2010 | 2012 | |
| Musculoskeletal pain | 2000 | 3.4451 | 2011 | 2014 | |
| Quality of life | 2000 | 6.2474 | 2011 | 2014 | |
| Functional status | 2000 | 4.9550 | 2011 | 2012 | |
| Postural control | 2000 | 4.8967 | 2011 | 2015 | |
| Chronic low back pain | 2000 | 3.1724 | 2012 | 2015 | |
| Trial | 2000 | 3.5618 | 2012 | 2013 | |
| Physical activity | 2000 | 4.3032 | 2012 | 2014 | |
| Reliability | 2000 | 3.2730 | 2012 | 2013 | |
| Movement | 2000 | 3.3155 | 2012 | 2014 | |
| Prognosis | 2000 | 4.5544 | 2012 | 2015 | |
| Association | 2000 | 3.2556 | 2012 | 2013 | |
| Roland morri | 2000 | 4.9577 | 2013 | 2015 | |
| Cross cultural adaptation | 2000 | 3.1499 | 2013 | 2015 | |
| Chronic pain | 2000 | 4.4235 | 2013 | 2016 | |
| Nonspecific low back pain | 2000 | 5.2072 | 2014 | 2015 | |
| European guideline | 2000 | 4.1641 | 2014 | 2015 | |
| Non-specific low back pain | 2000 | 7.1833 | 2015 | 2018 | |
| Physiotherapy | 2000 | 4.5874 | 2015 | 2016 | |
| Validity | 2000 | 6.7784 | 2015 | 2016 | |
| Spine | 2000 | 4.5707 | 2016 | 2018 | |
| Efficacy | 2000 | 3.9118 | 2016 | 2018 | |
| Adult | 2000 | 4.8871 | 2016 | 2018 | |
| Metaanalysis | 2000 | 4.9838 | 2016 | 2018 | |

FIGURE 8: Top 46 keywords with the strongest citation bursts.

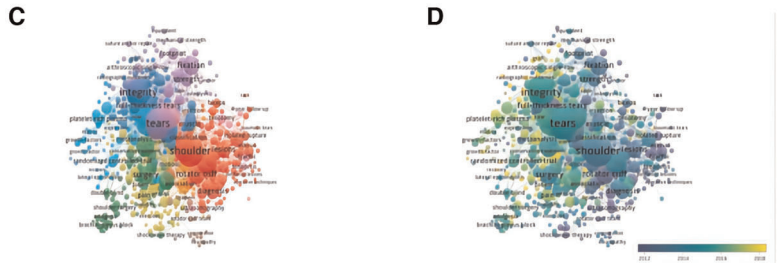



FIGURE 6
Keywords analysis of arthroscopic therapy of rotator cuff diseases related publications from 2002 to 2021. (**A**) Map of the top 30 most frequent keywords. (**B**) The dynamic growth of the top 50 most frequent keywords (Analysis based on the annual frequency). (**C**) The cluster map of the keywords subnetwork made by Vosviewer. (**D**) Distribution map of keywords according to the time of occurrence made by Vosviewer (blue-colored keywords occurrence earlier than the yellow ones).

"Glenoid Labrum" and so on. From Figure 6D, We can analyze the change in research topic in this field. "Superior Capsule Reconstruction", "Matrix Augmentation", "lateral Epicondylitis", "Mesenchymal Stem Cells", and "Pain Management" were hot keywords in recent years (Figure 6).

## The top 100 most-cited articles

The top 100 Most-Cited articles were mainly from AMERICAN JOURNAL OF SPORTS MEDICINE (34, 34%), JOURNAL OF BONE AND JOINT SURGERY-AMERICAN VOLUME (22, 22%), ARTHROSCOPY (21, 21%), JOURNAL OF SHOULDER AND ELBOW SURGERY (7, 7%), JOURNAL OF BONE AND JOINT SURGERY-BRITISH VOLUME (3, 3%), and others (13, 13%) (Figure 7A). Figure 7B showed that the top 100 Most-Cited articles were mainly produced between 2002 and 2018, however, there was no highly cited article produced in 2016. The article titled "The Outcome and Repair Integrity of Completely Arthroscopically Repaired Large and Massive Rotator Cuff Tears" published by Leesa M Galatz et al. in 2004 was the most highly cited article between 2002 and 2021 with a total citation of 1,263. We can learn the main information of the top 10 most highly cited articles in Table 1, there were 9 articles and 1 review.

# Bibliographic coupling analysis

## Journal

The VOSviewer was used to conduct the bibliographic coupling analysis of journals in this study. As shown in Figure 8A, 64 journals (Minimum number of documents of a source: 10) had a similar relationship with others. The top five journals with the biggest total link strength were ARTHROSCOPY-Journal of Arthroscopic and Related Surgery (Total Link Strength = 772,328 times), AMERICAN JOURNAL OF SPORTS MEDICINE (Total Link Strength = 702,069 times), JOURNAL OF SHOULDER AND ELBOW SURGERY (Total Link Strength = 668,842 times), KNEE SURGERY, SPORTS TRAUMATOLOGY, ARTHROSCOPY (Total Link Strength = 334,332 times), and JOURNAL OF BONE AND JOINT SURGERY-AMERICAN VOLUME (Total Link Strength = 244,256 times).

## Institution

The VOSviewer was used to conduct the bibliographic coupling analysis of institutions in this study. A total of 153 institutions (Minimum number of documents of an insttution: 10) were presented in Figure 8B. The institution with the biggest total link strength was Rush University (Total Link Strength = 197,813 times), followed by Seoul National University (Total Link Strength = 178,447 times), Hospital for Special Surgery (Total Link Strength = 152,643 times), Washington University (Total Link Strength = 112,718 times), and Sungkyunkwan University (Total Link Strength = 102,964 times).

## Country

There were 69 countries (Minimum number of documents from a country: 10) presented in Figure 8C made by VOSviewer. The United States ranked first with a total link strength of 2,067,291 times, followed by South Korea (Total Link Strength = 928,037 times), Germany (Total Link Strength = 661,973 times), France (Total Link Strength =

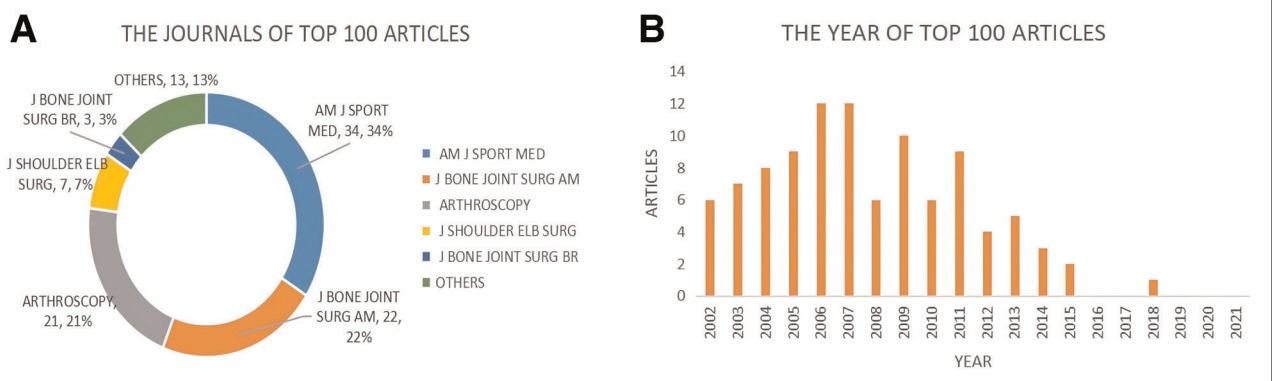



FIGURE 7
The Top 100 most-cited articles of arthroscopic therapy of rotator cuff diseases from 2002 to 2021. (A) The journal proportion of the top 100 most-cited articles. (B) The annual production of the top 100 most-cited articles.

TABLE 1 General information about the top 10 most-cited articles.

| Title | Type | Author | Year | Journal | Total citations | TC per year |
|---|---|---|---|---|---|---|
| The Outcome and Repair Integrity of Completely Arthroscopically Repaired Large and Massive Rotator Cuff Tears | Article | GALATZ LM | 2004 | J BONE JOINT SURG AM | 1263 | 66.4737 |
| Arthroscopic repair of full-thickness tears of the supraspinatus: does the tendon really heal? | Article | BOILEAU *P* | 2005 | J BONE JOINT SURG AM | 817 | 45.3889 |
| National trends in rotator cuff repair | Article | COLVIN AC | 2012 | J BONE JOINT SURG AM | 558 | 50.7273 |
| Repair integrity and functional outcome after arthroscopic double-row rotator cuff repair. A prospective outcome study | Article | SUGAYA H | 2007 | J BONE JOINT SURG AM | 519 | 32.4375 |
| The Reverse Shoulder Prosthesis for glenohumeral arthritis associated with severe rotator cuff deficiency. A minimum two-year follow-up study of sixty patients | Article | FRANKLE M | 2005 | J BONE JOINT SURG AM | 514 | 28.5556 |
| Functional and structural outcome after arthroscopic full-thickness rotator cuff repair: single-row versus dual-row fixation | Article | SUGAYA H | 2005 | ARTHROSCOPY | 455 | 25.2778 |
| Anatomical and biomechanical mechanisms of subacromial impingement syndrome | Review | MICHENER LA | 2003 | CLIN BIOMECH | 374 | 18.7 |
| Cuff integrity after arthroscopic versus open rotator cuff repair: A prospective study | Article | BISHOP J | 2006 | J SHOULDER ELB SURG | 368 | 21.6471 |
| Clinical results of arthroscopic superior capsule reconstruction for irreparable rotator cuff tears | Article | MIHATA T | 2013 | ARTHROSCOPY | 353 | 35.3 |

509,490 times), and Switzerland (Total Link Strength = 410,860 times) (Figure 8).

# Co-Authorship analysis

## Author

The VOSviewer was used to conduct the co-authorship analysis of authors in this study. There were a total of 174 authors (Minimum number of documents of an author: 10) were shown in Figure 9A. The largest total link strength author was Nikhil N Verma (Total Link Strength = 203 times), followed by Anthony A Romeo (Total Link Strength = 200 times), Brian J Cole (Total Link Strength = 133 times), Vincenzo Denaro (Total Link Strength = 120 times), and Peter J Millett (Total Link Strength = 112 times).

## Institution

A total of 148 institutions (Minimum number of documents of an organization: 10) were shown in Figure 9B analyzed by VOSviewer. The top five institutions with the biggest total link strengths were Steadman Philippon Research Institute (Total Link Strength = 108 times), Hospital for Special Surgery (Total Link Strength = 102 times), Rush University (Total Link Strength = 95 times), Washington University (Total Link Strength = 61 times), and Oregon Health and Science University (Total Link Strength = 61 times).

## Country

There were 38 identified countries (Minimum number of documents from a country: 10) presented in Figure 9C made by VOSviewer. The largest total link strength country was the United States (Total Link Strength = 416 times), followed by Germany (Total Link Strength = 174 times), Switzerland (Total Link Strength = 174 times), England (Total Link Strength = 170 times), and Canada (Total Link Strength = 129 times) (Figure 9).

# Co-citation analysis

## Publication

The co-citation analysis in our study was conducted by VOSviewer. There were a total of 850 publications (Minimum number of citations of a reference: 30) were shown in Figure 10A. The top five publications with the biggest total link strengths were as follows: "GALATZ LM, 2004, J BONE JOINT SURG AM, 10.2106/00004623-200402000-00002" (Total Link Strength = 14,845 times), "BOILEAU P, 2005, J BONE JOINT SURG AM, 10.2106/JBJS.D.02035" (Total Link Strength = 12,918 times), "GOUTALLIER D, 1994, CLIN ORTHOP RELAT R, 1994 Jul;(304):78–83." (Total Link Strength = 12,273 times), "GERBER C, 2000, J BONE JOINT SURG AM, 10.2106/00004623-200004000-00006" (Total Link Strength = 9,116 times), and "CONSTANT CR, 1987, CLIN

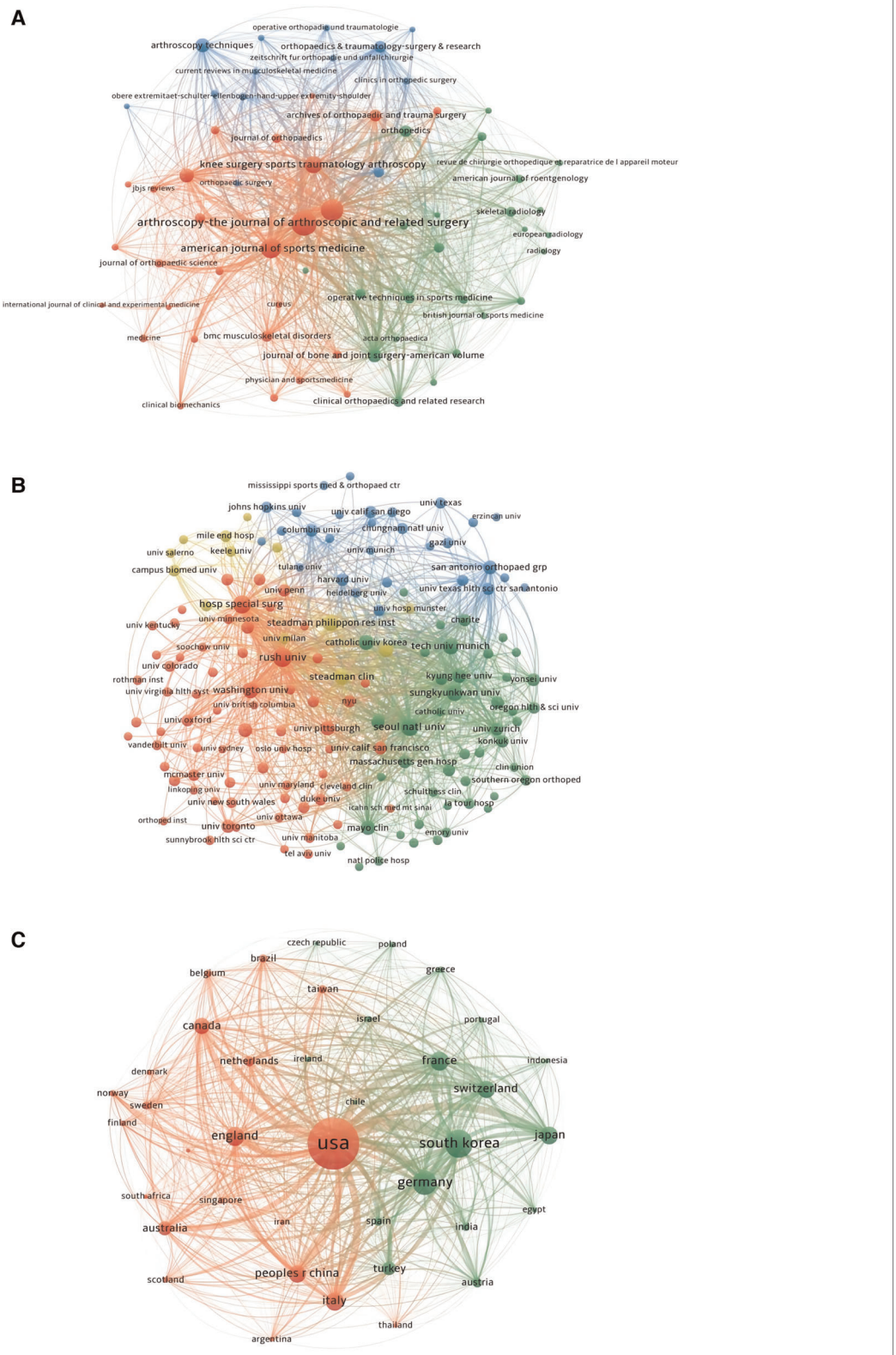



FIGURE 8
Bibliographic coupling analysis of journals, institutions, and countries (analysis based on the arthroscopic therapy of rotator cuff diseases related publications from 2002 to 2021). (**A**) Mapping of the 64 identified most relevant journals. (**B**) Mapping of the 153 identified most relevant institutions. (**C**) Mapping of the 69 identified most relevant countries.

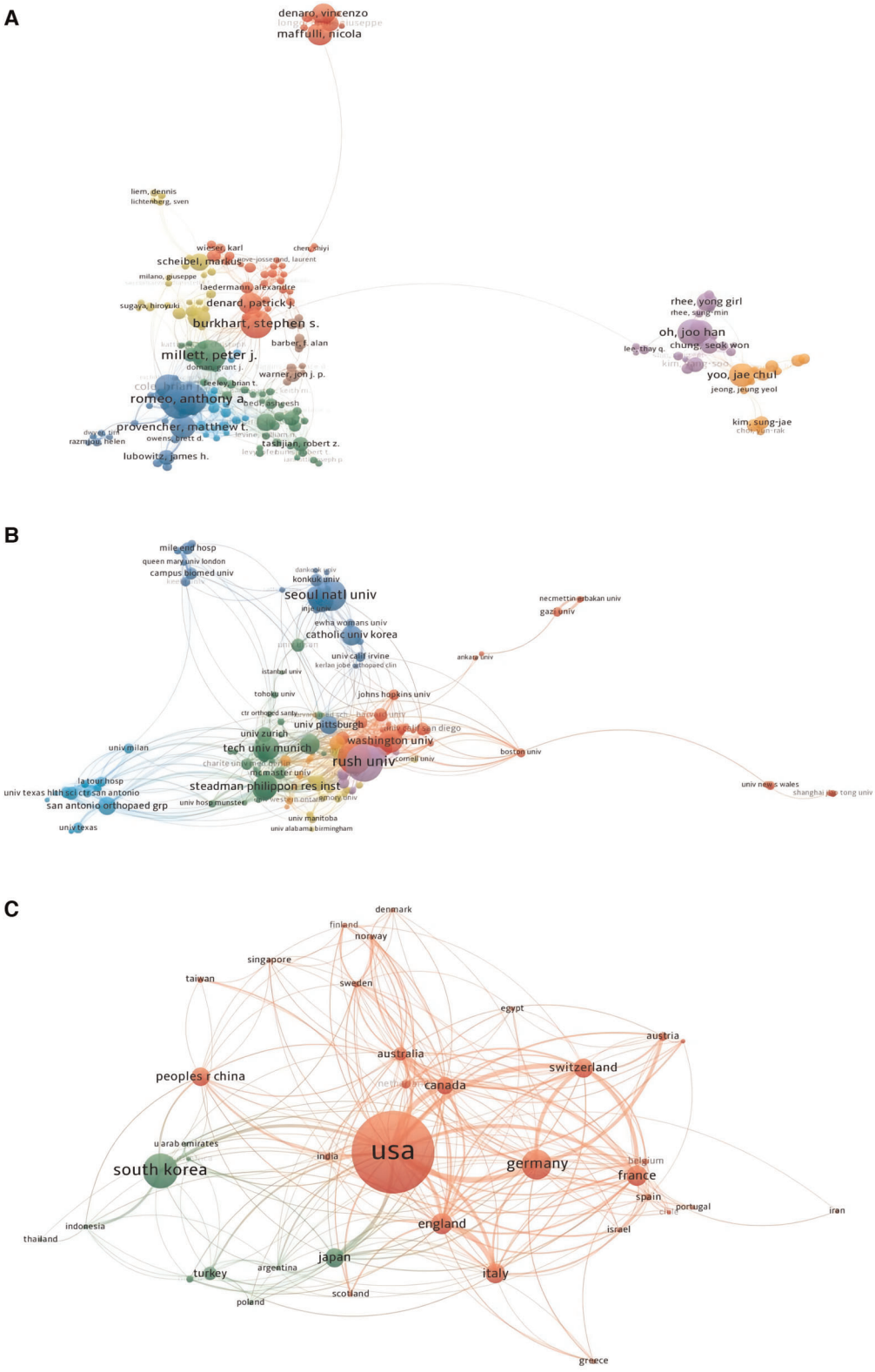



FIGURE 9
Co-authorship analysis of authors, institutions, and countries (analysis based on the arthroscopic therapy of rotator cuff diseases related publications from 2002 to 2021). (**A**) Mapping of the 174 identified the most relevant authors. (**B**) Mapping of the 148 identified the most relevant institutions. (**C**) Mapping of the 38 identified most relevant countries.

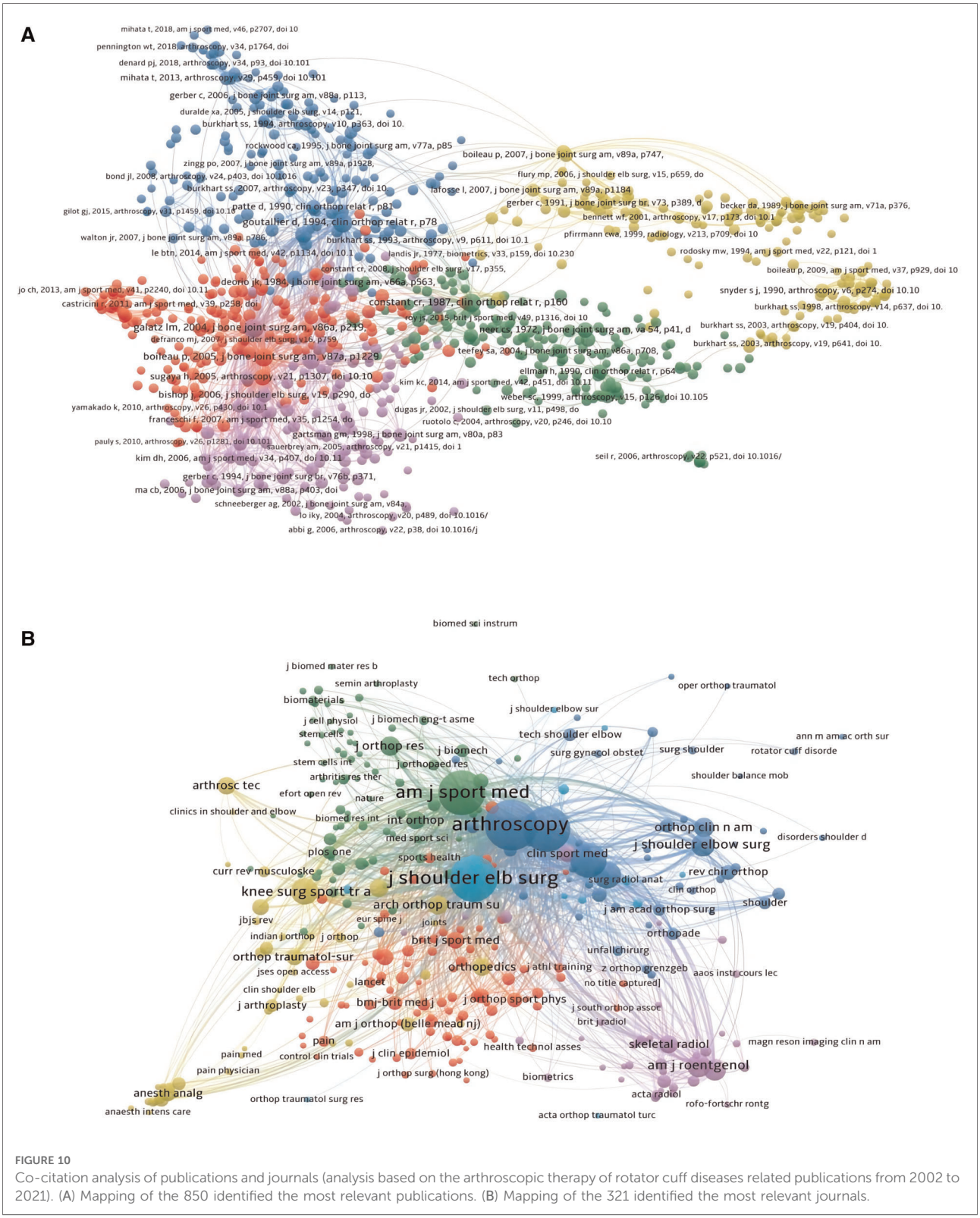



FIGURE 10
Co-citation analysis of publications and journals (analysis based on the arthroscopic therapy of rotator cuff diseases related publications from 2002 to 2021). (A) Mapping of the 850 identified the most relevant publications. (B) Mapping of the 321 identified the most relevant journals.

ORTHOP RELAT R, 1987 Jan; (214):160–4" (Total Link Strength = 9,026 times).

## Journal

There were 321 journals (Minimum number of citations of a source:30) presented in Figure **10B**. The largest total link strength journal was ARTHROSCOPY (Total Link Strength = 781,934 times), followed by JOURNAL OF SHOULDER AND ELBOW SURGERY (Total Link Strength = 692,203 times), JOURNAL OF BONE AND JOINT SURGERY-AMERICAN VOLUME (Total Link Strength = 659,225 times), AMERICAN JOURNAL OF SPORTS MEDICINE (Total Link Strength = 649,381 times), and CLINICAL ORTHOPAEDICS AND RELATED RESEARCH (Total Link Strength = 303,891 times).

# Discussion

## The purpose of bibliometric analysis on arthroscopic therapy of rotator cuff diseases-related publications

Bibliometric analysis is a powerful tool to analyze the research status and predict the future trend of a field in a certain period. Shoulder pain, mainly caused by rotator cuff diseases, accounts for about 16% of musculoskeletal disorders. This disease plagues millions around the world every year, especially the elderly and active athletes (13, 14). The emergence of arthroscopy techniques has contributed greatly to the management of rotator cuff diseases. The increasing interest in the Arthroscopic Therapy of Rotator Cuff Diseases-Related field has attracted more researchers and institutions dedicated to relevant research. In our study, the current status of Arthroscopic Therapy of Rotator Cuff Diseases-Related research, contributing countries and institutions, and the impact of authors and journals were analyzed by using methods of bibliometric analysis.

## Research Status of global publications

By using data visualization software, the results can be better presented to readers. As shown in the result section, there have been a dramatically increasing number of Arthroscopic Therapy of Rotator Cuff Diseases-Related publications in recent years. A linear regression model of the year and the number of publications was established based on the available data, which forecasts that more publications will be published in the following years.

The largest number of Arthroscopic Therapy of Rotator Cuff Diseases-Related publications produced between 2002 and 2021 were contributed by the United States. The academic impact of countries and institutions can be measured by the H-index and the total number of citations. The United States was also the country with the largest academic impact around the world. In a word, the United States can be regarded as the leader in the Arthroscopic Therapy of Rotator Cuff Diseases-Related field. Korea also has a great impact in this field, when considering the total number of publications and the total number of citations. Some countries, like France, the UK, Germany, Japan, China, Italy, and Canada, have also made a great contribution to this field because of their excellent scientific productions.

The majority of the most relevant institutions were located in the United States, including Steadman Philippon Research Institute, Rush University, Hospital for Special Surgery, Washington University, and so on. Among these institutions, Rush University contributed the largest number of publications compared with other American institutions. Seoul National University in Korea produced the largest number of Arthroscopic Therapy of Rotator Cuff Diseases-Related publications around the world between 2002 and 2021. In addition, Sungkyunkwan University and the Catholic University of Korea in Korea also made great contributions to this field.

Paying attention to the academic dynamics of the most relevant researchers can help to grasp the frontier research topic in the Arthroscopic Therapy of Rotator Cuff Diseases-Related field. The top 5 authors measured by the number of publications were Stephen S Burkhart, Peter J Millett, Anthony A Romeo, Nikhil N Verma, and Sae Hoon Kim. All of them can be seen as pioneers in this field. The academic impact of researchers can be evaluated by the H-index and G-index. Stephen S Burkhart was the most outstanding researcher in this field with the largest number of publications, as well as the highest H-index and G-index.

"ARTHROSCOPY-Journal of Arthroscopic and Related Surgery" published the largest number of publications in the past 2 decades. Considering the H-index and G-index of journals, ARTHROSCOPY was also the most impactful journal. In addition, AMERICAN JOURNAL OF SPORTS MEDICINE, JOURNAL OF SHOULDER AND ELBOW SURGERY, KNEE SURGERY, SPORTS TRAUMATOLOGY, ARTHROSCOPY, and JOURNAL OF BONE AND JOINT SURGERY-AMERICAN VOLUME were excellent journals with great impact in this field. In the future, more relevant high-quality research publications may be found in these journals.

By using the method of bibliographic coupling analysis, relationships between publications in terms of journals, institutions, and countries can be investigated. The result showed that ARTHROSCOPY was the most relevant journal, Rush University was the most relevant institution, and the United States was the relevant country. The co-authorship

analysis can provide information about the relationship of the items by analyzing the number of their co-authored documents, which can present the collaborative relationships among authors, institutions, and countries. Nikhil N Verma was an active researcher in this field, who was more likely to cooperate with other researchers. Steadman Philippon Research Institute established the widest cooperation relationships with other institutions around the world. And the United States had the widest cooperation with other countries. Co-citation analysis can be used to identify the relationship of items by analyzing the number of times they were cited together. The publication titled "The outcome and repair integrity of completely arthroscopically repaired large and massive rotator cuff tears" produced by Leesa M Galatz et al. in 2004 can be seen as a landmark study in the Arthroscopic Therapy of Rotator Cuff Diseases-Related field. ARTHROSCOPY was the journal with the highest cited times in this field.

## Current questions in the field of arthroscopic therapy of rotator cuff diseases

Massive rotator cuff tears refer to tears of tendon maximum diameter greater than 5 cm or tears of two or more tendons (15). Repair of massive rotator cuff tears by arthroscopic therapy is technically safe and feasible. However, there are several significant challenges for the orthopedic surgeon, such as inelastic poor-quality tendon tissue, scarring, fatty infiltration, and muscle atrophy (16). Keywords analysis showed that words like "Superior Capsule Reconstruction", and "Fascia Autograft Patch", indicated that multiple techniques were investigated to treat massive irreparable rotator cuff tears. Treatment strategies range from non-operative to surgical options, including debridement, partial repair, complete repair utilizing margin convergence and interval slides, tendon transfers, arthrodesis, and Reverse Total Shoulder Replacement (RTSA). Choosing treatment options based on indications is crucial to achieving the best outcomes for patients with massive rotator cuff tears (17). For patients with massive and irreparable rotator cuff tears, significant pain and dysfunction have a serious impact on the quality of life of the patients. However, there is no gold standard for non-operative treatments (18). This question is worthy of further study and exploration for researchers. Chronic degenerative rotator cuff disease is commonly recognized as an age-related, intrinsic, degenerative disease, which is also a concern for orthopedic surgeons. Studies showed that tear enlarges over time and worse pain are common in patients with chronic degenerative rotator cuff diseases. Non-operative therapeutic efficacy is frequently below expectation and surgical intervention is necessary. Those patients have limited healing potential and a high risk of recurrence after procedures (19). The severity of muscle atrophy and fatty infiltration are height correlated with the postoperative probability of tendon retear (20). In addition, rehabilitation and physical activity after arthroscopic procedures are the main concerns for both patients and surgeons. There are still controversies about the recommended postoperative rehabilitation protocol. Consistently, passive motion in the early stages is a controversial topic. Early passive motion rehabilitation can prevent postoperative stiffness, fatty infiltration, and muscle atrophy theoretically, but may also delay tendon healing. Further studies will be required to evaluate different rehabilitation protocols credibly and comprehensively.

## Future research trends of the arthroscopic therapy of rotator cuff diseases-related field

A visual knowledge map of keyword co-occurrence can help to identify the keywords that could reflect research trends in the related field. In **Figure 6C**, Each node represents a keyword, the size of the node is associated with the frequency of the keywords occurrence counts, the link between two nodes represents the co-occurrence of the two keywords, and different colors represent different clusters. All the keywords from 2002 to 2021 were divided into 6 clusters: Basics Anatomy and Diagnostics Related Study, Epidemiological Study including retrospective study and cohort study, Arthroscopic Technique Related Study, Postoperative Rehabilitation Related Study, Intra-Articular Injection Related Study, Rotator Cuff Diseases Combined with Other Shoulder Disorders Related Study. **Figure 6D** showed the relationship between occurrence years and keywords. The color changes from blue to yellow with occurrence years. Blue-colored keywords occurrence earlier than the yellow ones. Keywords with high occurrence frequency in recent years, such as "Apoptosis", "oxidative stress", "Inflammation", and "Animal Model", indicated that basic research is still popular with researchers in this field. In recent years, Yoshiaki Itoigawa et al. studied the relationship between recurrent tears after arthroscopic rotator cuff repair and superoxide-induced oxidative stress (21). Se-Young Ki et al. studied the relationship between fatty infiltration and gene expression in patients with medium rotator cuff tears (22). Sung-Min Rhee et al. studied hematologic expression in patients who underwent arthroscopic rotator cuff repair (23). These words with high occurrence frequency recently, like "Platelet Rich Plasma", "Small-Intestine Submuc Stem Cell", and "Mesenchymal Stem cell" indicated that intra-tendinous injection therapies were research hot topics in the related field

(24). Rotator cuff diseases were challenges to the orthopedic surgeon. More and more new arthroscopic techniques were developed to improve the healing potential and initial strength of rotator cuff repair (RCR) in recent 2 decades. The Single-Row Fixations included Two-Simple Fixations, Arthroscopic Mason-Allen Fixations, and Massive Cuff Stitch. It was considered that the Double-Row repair had a higher ultimate tensile load compared with the single-row repair. Among the single-row fixations, the Massive Cuff Stitch had similar cyclic and load-to-failure characteristics to the Double-Row Fixation (25). Studies showed that double-row repair has a significantly higher rate of intact tendon healing compared to single-row repair, especially in patients with large or massive rotator cuff tears. However, there was no significant difference in clinical functional improvement. Therefore, the double-row repair should be used only in selected patients (26, 27). Suture-bridge double-row (SB-DR), a simplified double-row fixation, is considered to have superior biomechanical properties, greater footprint contact area, and pressure (28). Southern California Orthopedic Institute row (SCOI row) is a single-row arthroscopic technique, which uses triple-loaded anchors to achieve RCR. Studies showed that SCOI rows have better biomechanical properties compared to the SB-DR (29). In addition, words in **Figure 6D**, like "Opioid", "Pain", and "Acetaminophen", showed postoperative pain management in patients undergoing RCR was popular with researchers. A fully functioning and painless shoulder joint is a vital rehabilitation target after arthroscopic therapy. Besides rehabilitation and physical activity, postoperative pain management is a vital issue and deserves further reflection. There were studies revealing that postoperative pain was associated with shoulder stiffness after arthroscopic rotator cuff repair. Therefore, strategies for early postoperative pain relief may help to decrease rate of postoperative shoulder stiffness (30). More publications on postoperative pain management may be published in the next few years.

## Limitations

By using the methods of bibliometric analysis, the most valuable publications, top journals, major researchers, and contributing countries were analyzed in the Arthroscopic Therapy of Rotator Cuff Diseases-Related field. However, there are some limitations that we must clarify. First, we used the WoSCC database as the database source, which may cause bias due to the database variation. Second, only English language publications retrieved from the WoSCC were analyzed. Language bias may exist in our study because of ignoring of Non-English language publications. The results may differ from the actual research condition because some latest published outstanding publications may be ignored because of their low cited times. Therefore, the latest published and Non-English language publications are also necessary for daily Bibliometric Analysis Related research.

## Conclusion

Arthroscopic Therapy of Rotator Cuff Diseases Related research presented a rising trend in the past 2 decades. The United States can be regarded as the leader because of its huge contributions to this field. The journal ARTHROSCOPY published the largest number of publications in this field. It can be predicted that research about advanced arthroscopic techniques and postoperative pain management of patients with rotator cuff diseases will be the next research hotspots in the following years.

## Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author/s.

## Ethics Statement

Ethics approval was not applicable, All data comes from the public database.

## Author contributions

HFJ wrote the manuscript. WYW and RXY revised this manuscript. YLD, HM and WQX prepared the figure. HZL prepared the table. WFX and YSL conceptualized this research and decided on the content. All authors approved the final version of the manuscript and agreed to be accountable for all aspects of the work. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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# Present situation and development prospects of the diagnosis and treatment of rotator cuff tears

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Rotator cuff tears are an important cause of shoulder pain and are caused by degeneration or trauma of the shoulder tendon at the anatomical neck of the humeral head. The understanding and research of rotator cuff tears have a history of hundreds of years, and their etiology, diagnosis, and treatment have a complete system, but some detailed rules of diagnosis and treatment still have room for development. This research paper briefly introduces the diagnosis and treatment of rotator cuff tears. The current situation and its valuable research direction are described.

KEYWORDS

rotator cuff tear, musculoskeletal ultrasound, arthroscopy, glucocorticoid, minimally invasive surgery

## 1. Introduction

The rotator cuff muscle group is composed of the subscapular, teres minor, supraspinatus, and infraspinatus muscles. Its tendon forms a sleeve-like structure at the anatomical neck of the humeral head. The most important function of the rotator cuff is to ensure the stability of the shoulder joint (1). The estimated prevalence of shoulder pain in the population is approximately 16%–34% (2, 3), and rotator cuff problems are one of the main causes of shoulder pain. According to the statistics conducted by the U.S. Department of Health and Human Services in 2004, the number of visits caused by shoulder pain was approximately 4.5 million, and the number of rotator cuff surgeries was up to 20,000 (4). Therefore, public health problems caused by rotator cuff tears are common and important. The diagnosis and treatment of rotator cuff tears is a focus of clinical medicine, especially orthopedics.

## 2. Pathogenesis

At present, etiological research on chronic rotator cuff tears can be summarized into two kinds: degenerative changes or exogenous impacts.

As early as 1934, Codman proposed that the main cause of rotator cuff tears was tendon degeneration (5). Rothman performed rotator cuff angiography in 1965 and found that the tendons of the supraspinatus and infraspinatus muscles had clear ischemic areas, and ischemia led to the degeneration of the tendons, resulting in a decrease in rotator cuff strength, injury, and tear (6). In 1972, Neer questioned the theory of degenerative change (7). He suggested that 95% of rotator cuff tears were caused by acromion impact. The

movement of the shoulder joint causes the rotator cuff to be slightly impacted by the acromion and coracoacromial arch, resulting in congestion and edema of the rotator cuff, which may eventually lead to tendon rupture (8).

Therefore, the incidence rate of rotator cuff tears increases with age (9). At the same time, for occupations requiring a wide range of upper limb activities, especially throwing athletes, the probability of rotator cuff tears in youth is significantly higher than that in the general population (10). In addition, a study involving 180 patients with rotator cuff injuries (11), showed that diabetes, obesity, hyperlipidemia, hypertension, and smoking habits were risk factors for rotator cuff injury.

# 3. Clinical manifestation

## 3.1. Symptom

The most common complaints of patients with rotator cuff tears are pain and fatigue. The pain site is mainly around the deltoid muscle, and the pain is usually aggravated when the upper limb moves widely or the shoulder is compressed (12). However, in subsequent studies, the correlation between pain and rotator cuff tears was questioned. First, in Itoi's study (13), the main cause of shoulder pain was synovial inflammation caused by rotator cuff tears, not tendon injury. Another series of studies pointed out that the severity of rotator cuff tears seems to have little relationship with the severity of pain, and more than half of rotator cuff tears have no symptoms (14). Compared with complete tears and partial tears, the traditional understanding is that complete tears will bring more severe pain (15), but some studies also reported that the tear range will not affect the pain index (16) or that the pain caused by partial tears is higher than that caused by complete tears (17). Therefore, the significance of shoulder pain in the diagnosis of rotator cuff tears remains to be further discussed.

Because rotator cuff tears are essentially tendon injuries, shoulder fatigue is also one of the common complaints of patients with rotator cuff tears. For complete or large-area tears, fatigue is a particularly important symptom (18). It should be noted that when distinguishing between rotator cuff tears and fatigue caused by pain, such as synovitis and osteoarthritis, local anesthetics are often used to check muscle strength after injection. Fatigue caused by rotator cuff tears will not be relieved by local anesthesia.

## 3.2. Physical examination

There are various physical examination methods for the shoulder, and the effect of those methods varies greatly. Therefore, there is no perfect examination method to accurately diagnose rotator cuff tears. In 2005, Park et al. conducted a study involving 552 patients (19) and using arthroscopy as the diagnostic standard, they verified eight common shoulder joint examination methods, of which three were selected as the diagnostic examination methods of rotator cuff tears: active painful arc test, drop arm test, and weakness in external rotation. The combination of the three methods can achieve high diagnostic efficiency. If the three methods were positive, the final diagnosis was a rotator cuff tear, whose likelihood ratio was 15.6. However, if the three methods were negative the final diagnosis was no rotator cuff tear, whose likelihood ratio was 0.16, meaning that the scheme can achieve quite a good diagnosis or exclusion effect. Therefore, these three inspection methods are the most commonly used in a large number of physical examination methods. Another study pointed out that the Hornblower sign, that is, shoulder joint external rotation pain when resisting applied force, can be used alone for the examination of rotator cuff tears, and the sensitivity can reach 70% (20).

However, at present, research on shoulder physical examination is still insufficient. There is not enough high-quality evidence in evidence-based medicine to determine one or a group of examination methods that can effectively diagnose rotator cuff tears (21). Therefore, relevant research needs to be further promoted, and the clinical diagnosis needs to be combined with the medical history, imaging, and other methods.

## 3.3. Imaging examination

### 3.3.1. X-ray

At present, x-ray is not routinely used in the clinical diagnosis of rotator cuff tears, especially chronic rotator cuff tears. However, an x-ray can detect the relative position changes of the humeral head and acromion, which is helpful to diagnose complete tears. An image of a noticeable humeral displacement can confirm a large-scale tear and, at this time, the rotator cuff tendon can be fully involved (22). Although x-rays do not satisfactorily meet the current imaging needs, with the progress at the medical level, the diagnostic ability of rotator cuff injury still has a certain value in rural clinics lacking medical conditions.

### 3.3.2. Musculoskeletal ultrasound (MSK US)

Compared with other imaging techniques, ultrasonography has inherent advantages: no radiation, low cost, and convenient bedside examination (23). Some clinicians who have received ultrasound training can use MSK US for rapid and accurate initial evaluations (24). In a study that included 331 cases of rotator cuff surgery (25), taking the surgical results as the gold standard, MSK had a sensitivity of 79% and a specificity of 94%. In addition, many diagnostic studies have shown that MSK is a very effective diagnostic method (26–28). The manifestations of rotator cuff tears in MSK US include but are not limited to tendon thickening with hypoechoic, tendon calcification, tendon fiber rupture, and steatosis (29).

### 3.3.3. MRI

MRI is very sensitive to soft tissue injury, so it can be used to diagnose rotator cuff tears. It is effective in the diagnosis of complete tears, but many studies suggested that the sensitivity of

MRI to partial tears is not enough to meet diagnostic needs (30, 31). In patients with rotator cuff tears, MRI findings include but are not limited to tendon discontinuity, fluid signal generation, acromial osteophyte generation, and rotator cuff atrophy (32). A further diagnostic method is MR arthrography. When the MRI image is normal but there is a clinical suspicion of a rotator cuff tear, MRI can be used to observe whether the contrast agent goes deep into the acromion space or subdeltoid space after the intra-articular injection of the gadolinium contrast agent.

From the perspective of comprehensive imaging examination, the combined use of multiple imaging can more accurately diagnose most patients with rotator cuff tears, but there are still deficiencies compared with other common orthopedic diseases, especially fractional rotator cuff tears. It is suggested that comprehensive imaging examination, medical history, and physical examination should be combined to help in the diagnosis (33).

# 4. Treatment

The treatment of rotator cuff tears depends on many factors, such as tear range, tear time, shoulder joint mobility, and patient age (34). For such a surgical disease, the focus of research is whether surgery can be beneficial. In most current studies, even in patients with complete tears, the benefit of surgical treatment is not clearly higher than that of conservative treatment (35, 36). In an observational study of 4,542 patients with complete tear (37), functional improvement was not related to the treatment regimen after 1 year of intervention. However, in another long-term follow-up study (38), compared with the scores of function and symptoms after 10 years of intervention, surgical intervention was significantly better than conservative treatment. The explanation of the abovementioned results may be the instability of the area with the tear or tendon steatosis (39), but this was not confirmed by rigorous pathological tests in the current study. At present, the only patient population strongly recommended for surgical treatment is young patients with acute complete tears with severe symptoms and limited function.

## 4.1. Conservative treatment

The main purpose of conservative treatment after rotator cuff tears is to reduce symptoms and improve function (40). However, in patients with chronic tears, due to uncertain surgical indications, the effective rate of definite improvement within 1 year ranges from 33% to 92% (41). The key point of conservative treatment is rehabilitation exercise for the tissues near the shoulder joint. In the early stage, the joint capsule was stretched to improve the joint range of motion. In the middle stage, self-weight or light resistance exercise is used to restore muscle strength, and in the later stage, all-around shoulder training is carried out to improve joint coordination (42). Rehabilitation exercises should gradually change from passive exercise to active exercise. To restore function, rehabilitation exercises should be carried out as soon as possible. Theoretically, the treatment plan should be adjusted according to the degree of tear, muscle atrophy, and patient needs, but some studies have pointed out that adjusting the treatment plan for partial tear and complete tear has little effect on functional rehabilitation (40). In the clinical trial conducted by Zhang et al. (43), it was confirmed that active and passive shoulder joint activities can effectively promote tendon healing and improve shoulder joint function. Sheard et al. (44) added muscle strength training and nerve coordination training based on joint function training to achieve a better rehabilitation effect. Mahure et al. (45) used transcutaneous electrical nerve stimulation (TENS) for patients with rotator cuff injury in rehabilitation, and the results showed that inflammation and pain were effectively controlled, which could, to some extent, replace traditional analgesic methods. In the clinical research conducted by Bennell et al. (46), patients were completely allowed to practice after learning the exercise program by themselves, and the rehabilitation effect was not significantly different from that of the auxiliary treatment of the rehabilitator.

In addition to rehabilitation training, rotator cuff injury can benefit from glucocorticoid injection: to a certain extent, it can reduce local inflammatory reactions and relieve pain. Early injection of glucocorticoids after acute tear can quickly and effectively relieve pain and improve function, but it has no therapeutic effect on rotator cuff injury itself (47). Studies have shown that glucocorticoid injection therapy has better short-term efficacy and safety than placebo, oral non-steroidal anti-inflammatory drugs, and physical therapy in pain relief, activity, and function improvement (48).

In most cases, after the broken ends of tendons are repaired and sutured by surgery, the broken ends can be repaired and healed well within 6 weeks. However, several studies have shown that tendon rupture caused by glucocorticoids has poor repair and healing between the broken ends after surgical repair, and it easily ruptures again in the long term (49, 50). This shows that glucocorticoids can not only lead to spontaneous rupture of the tendon but also reduce the repair function of the tendon itself, and its mechanism is not clear yet (51). Spontaneous rupture of tendons caused by glucocorticoids has always been a very difficult problem in the field of sports medicine. In the 2019 clinical guidelines (52), moderate evidence supports that a single injection of corticosteroids combined with local anesthetics can improve the pain and function of patients with shoulder pain in the short term. At the same time, it is necessary to pay attention to the negative effects of multiple injections of corticosteroids on rotator cuff tissue.

In addition, massage, acupuncture, local injection of nitroglycerin, and other methods will also be used to treat rotator cuff tears in the clinic (53). Because the therapeutic effect has not been confirmed by sufficient data, it will not be discussed here. In addition, it should be noted that in some patients with rotator cuff tears treated conservatively, the severity of tears will gradually increase. Pain or fatigue will increase (54), and clinically, it will aggravate muscle injury and increase the difficulty of treatment. Therefore, it is recommended that all

patients treated conservatively should have shoulder physical examination and imaging examination every 6–12 months (55).

## 4.2. Surgery treatment

At present, there are three common surgical methods: open surgery, small incision surgery, and arthroscopic surgery. In open surgery, the deltoid muscle needs to be completely open and then sutured after the rotator cuff tendon is exposed as much as possible. After rotator cuff injury, surgical injury of the deltoid muscle will cause the affected shoulder to completely lose function for a period of time (56), and the risk of infection is high. Therefore, compared with other less invasive surgical methods, open surgery has rarely been used.

Small incision rotator cuff repair was systematically applied by Levy in 1990 (57). Compared with open surgery, it has fewer intraoperative deltoid injuries, a good rotator cuff reconstruction effect, an obvious improvement in early postoperative quality of life, and a significantly shortened hospital stay (58). In a long-term follow-up study (59), patient satisfaction and treatment effect were basically the same as with arthroscopic treatment.

Arthroscopic repair of rotator cuff tears is the most widely used technique. Arthroscopy has natural advantages, including a small incision, a clear surgical field, small muscle injury, and a low infection rate (60). With the gradual upgrading of arthroscopic instruments and the improvement of arthroscopic operation technology, its clinical efficacy is also improving. At present, there are many methods of arthroscopic repair. The use of suture anchors, patches, tendon nails, and other auxiliary materials can effectively improve the repair effect (61).

As the trauma caused by arthroscopy is small and the postoperative inflammatory reaction is weak, in the research conducted by Kang (62) and Cho (63), the postoperative pain of arthroscopic surgery was far less than that of open surgery, which is significant for postoperative rehabilitation training. In addition, Nazari conducted a meta-analysis (64) on the range of motion of the shoulder joint after surgery, and the results showed that both arthroscopy and open surgery could achieve good improvement. As for shoulder joint function, the clinical research conducted by Walton et al. (65) showed that the recovery speed of shoulder joint function after arthroscopic surgery is much faster than that of open surgery, which is closely related to the small trauma brought about by arthroscopy. As the main method of rotator cuff tear surgery, multifaceted research on arthroscopic repair surgery is still in progress and has broad development prospects.

For massive rotator cuff injuries that cannot be repaired directly by tendons, tendon transfer is a therapeutic option that can effectively improve the function of the shoulder joint. In 1988, Gerber et al. (66) first applied this surgical method to separate the latissimus dorsi tendon from the humerus and fix it at the greater tubercle of the humerus to replace the broken supraspinatus and infraspinatus muscles. In 2012, a meta-analysis (67) showed that latissimus dorsi transfer could effectively improve shoulder joint range of motion and muscle strength, and the Constant shoulder joint score increased from 56 to 80 on average. For the anterior rotator cuff injury, such as subscapularis, the operation of pectoralis major muscle transfer can be selected. In a prospective follow-up study conducted by Moroder (68), the patients receiving pectoralis major muscle transfer surgery had significant recovery of shoulder joint range of motion within 10 years, especially the internal rotation movement. Pain relief and shoulder joint function scores were improved as well. In addition to the two most commonly used methods, trapezius, teres major, deltoid, and pectoralis minor can be used for tendon transfer, which can be adjusted according to the specific location of the injury. The main limitation of tendon transfer in rotator cuff injury is that the transferred tendon is prone to rupture or partial rupture, resulting in poor surgical effect, local hematoma, frozen shoulder, and other complications (69).

In addition to tendon transfer, various surgical methods can also be used for massive irreparable rotator cuff tears so that patients receive satisfactory treatment. Gartsman (70) reported a 79% satisfaction rate after open debridement and subacromial decompression in patients with massive irreparable rotator cuff tears. This kind of operation will decrease the pain of patients and improve the range of motion of shoulder joints and the ability to do daily tasks but will cause muscle strength decline (71), so it is more suitable for elderly patients with low functional requirements. Because of tendon retraction or excessive tissue tension, partial rotator cuff repair can also be the treatment option for huge rotator cuff injuries (72). Moser et al. (73) compared the surgical effects of complete repair and partial repair, and found that in patients with massive rotator cuff tears, a complete repair would bring a greater range of motion of the shoulder joint, while there was no statistical difference between pain and functional scores, which are more critical for the evaluation of surgical effects. In addition, there is the option of using auto-graft fascia lata as a patch to restore the superior capsule to its physiological state (74). Minhata et al. (75) followed up on the patients who underwent the superior capsule reconstruction for 2 years and found that the function of the shoulder joint was significantly improved, and there was no report of complications such as postoperative adhesion.

The subacromial spacer is another effective method for treating massive rotator cuff injuries. It uses arthroscopy to place biodegradable implants between the acromion and the humeral head, reducing friction between the rotator cuff injury site and the bone structure (76). While relieving pain, it also increases the abduction force arm of the shoulder joint, restoring the shoulder joint function. In the clinical cohort of Piekaar et al. (77), during a 3-year follow-up period, all 44 patients showed good pain relief and functional improvement. In a systematic review conducted in 2019 (78), the adverse reaction rate of this treatment method was only 3%, and the Constant-Murley shoulder joint function score was still satisfactory 2–3 years after surgery. However, in the study by Ruiz Ibán et al. (79), the patient satisfaction rate for this treatment method was only 40%, with 31.3% of patients experiencing increased pain 10 months after surgery and requiring a second surgery. Therefore, the effectiveness and safety of subacromial spacers are currently unclear.

Finally, reverse total shoulder arthroplasty (rTSA) can also be used as one of the treatment options for massive irreparable rotator cuff tears. Although rTSA can improve the pain and functional limitation of massive rotator cuff tears (80), its application is limited by the high rate of complications and revisions (81), so it is not recommended to use this surgical method in young patients (82).

During postoperative recovery, there are reports of the use of bioactive substances to promote the biological healing of rotator cuff tendons, such as platelet-rich plasma, mesenchymal stem cells, and cytokines gel. In cytological studies and animal experiments, PRP achieved beneficial results (83). In a meta-analysis that included 1,045 clinical data (84), PRP reduced the failure rate of rotator cuff injury surgery by more than 25%. However, in some clinical randomized trials, the effects of PRP on pain, function, and postoperative recovery were not statistically significant (85, 86). Gulotta et al. (87) demonstrated the repair ability of MSCs using the mouse rotator cuff injury model. In the clinical research conducted by Hernigou et al. (88), MSCs not only improved the degree of postoperative biological healing but also reduced the incidence of secondary laceration during the 10-year follow-up. The high expression of some cytokines, especially TGF-β3, in fetal trauma is believed to be related to scarless repair (89). In the mouse rotator cuff injury model of Han et al. (90), the gel containing TGF-β3 achieved a beneficial adjuvant therapeutic effect after injection. However, relevant research has not yet entered the clinical stage.

## 5. Summary

Rotator cuff tears have been recorded for a long time and are common in the population, especially asymptomatic rotator cuff tears. The etiology is clear, and the clinical diagnosis of complete tears and wide-range tears is relatively simple, but the identification of single tendon tears is still challenging and needs to be combined with several physical examinations and imaging to obtain a comprehensive diagnosis. The treatment is mainly conservative to maintain and restore function and surgical treatment with arthroscopic repair is the main treatment. Although the surgical indications are not completely clear, there is a great difference between young patients with definite symptoms and elderly patients with chronic tears. At present, the directions that are considered to be of more research value include efficient clinical diagnosis methods, more methods of conservative treatment, research related to arthroscopic surgery, and assisted recovery with platelet-rich plasma or mesenchymal stem cells.

## Author contributions

TZ: conceptualization; investigation; original draft; review and editing. CH: review and editing XW: supervision. All authors contributed to the article and approved the submitted version.

## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



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