A Bibliometric Analysis of Cleft Lip and Palate-Related Publication Trends From 2000 to 2017

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Abstract
Objective: Cleft lip and palate (CLP) is the most common human cranial and maxillofacial birth defect. The aim of this bibliometric analysis was to provide an overview of the development of CLP-related research.

Method: Cleft lip and palate-related studies published from 2000 to 2017 were retrieved from the Science Citation Index Expanded core database. Publication date, journal, authors, first authors, keywords, and citations were extracted and quantitatively analyzed using Bibliographic Item Co-Occurrence Matrix Builder software. The word matrix and co-occurrence matrix were established, and the co-citation analysis, keyword clustering, and social network analysis (SNA) of highly cited papers were completed.

Results: A total of 9040 articles were retrieved from the 18 years of publications that were searched. The number of documents steadily increased over the period of interest, with a slight decrease in 2016 and 2017. This article separately examined the top most cited papers and high-frequency keywords from 3 time periods: 2000 to 2005, 2006 to 2011, and 2011 to 2017. The strategy coordinates of citation reflect TGF-β3, MSX1 gene, technique for cleft lip repair, TTF2, P63, IRF6 gene, FGF signaling, PVRL1, TGFBR2, and BMP4 gene as areas of research interest in the field. Moreover, the SNA of keywords highlighted new research topics: meta-analysis, cone beam computed tomography, tooth agenesis, case–control study, association study, micrognathia, DiGeorge syndrome, NSCL/P, UCLP, GWAS, MTHFR, and CLPTM1L.

Conclusion: We conducted bibliometric research of CLP across an 18-year span. The results help to define an overall command of the latest topics in CLP and provide insight for launching new projects.

Keywords
bibliometric, cleft lip and palate, strategic diagram, social network analysis

Background
Cleft lip and palate (CLP) is the most common human cranio-maxillofacial birth defect. Cleft lip and palate is a group of complex diseases that is caused by interactions of environmental and genetic factors. Cleft lip and palate is a congenital malformation, and it may negatively impact several facets of children’s function and development, including sucking and eating, facial appearance, language development, mental health, and social interaction. These and other aspects of CLP are due to soft tissue malformations and varying degrees of bone tissue defects. Surgical repair is the only treatment for CLP. However, postoperative orthodontic and orthognathic treatment, voice training, psychological intervention, and a series of treatment measures place huge burdens on the affected children, their families, and society (Dixon et al., 2011; Burg et al., 2016).

Epidemiological studies have shown that the incidence of CLP is related to geographical, ethnic, environmental, and

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socioeconomic conditions. The worldwide incidence is approximately 1 in 700: The incidence is highest among Asians and American Indians (1 in 500), moderate among Caucasians (1 in 1000), and lowest among Africans (1 in 2500). The male to female gender ratio of CLP is approximately 1.5 to 2.0:1 (Shi et al., 2007). The prevalence of CLP among Chinese neonates is 1.42 in 1000 (Dai et al., 2010).

Cleft lip and palate often has an unclear etiology. It can occur alone, but it can also occur as part of a wide range of chromosomal abnormalities, inherited genetic disorders, or teratogenic syndromes. Cleft lip and palate can be classified according to the affected anatomical site: cleft lip only (CLO), CLP, and cleft palate only (CPO). Among these classifications, CLO and CLP are often combined into a single group: cleft lip with or without cleft palate (CL/P; Leslie and Marazita, 2013). Cleft lip and palate can also be classified as syndromic and nonsyndromic on the basis of congenital malformations associated with other sites. Approximately 50% of CPO is syndromic and 70% of CL/P is nonsyndromic.

Presently, treatment for CLP requires multidisciplinary care, including specialties of cosmetic surgery, nursing, maxillofacial surgery, otolaryngology, speech therapy, audiology, psychological counseling, genetic testing and counseling, dentistry, and orthodontics. Treatment regimens need to continue from birth to adulthood and, sometimes, even to older age (Alansari et al., 2014; Stock et al., 2015; Burg et al., 2016; Hamlet and Harcourt, 2017).

Bibliometric analysis is a relatively complete information science research method, merging science with mathematical and statistical methods to quantitatively analyze knowledge and information. With bibliometric analysis, we can equate the growth and impact of scientific literature, knowledge trends, and processes within academic fields and develop specific public health-care plans (Arunachalan and Gunasekaran, 2002; Moodley et al., 2015; Zhao et al., 2018).

Citation analysis is one of the most commonly used methods in bibliometrics. The co-citation and co-word analyses of the literature reflect the interrelation between articles; highly cited papers reflect the research interests of certain periods; and high-frequency keywords represent the current areas of interest (ie, “hot topics”) within research. Cluster analysis has been widely used to extract research themes within a research field (Li et al., 2015). Specifically, hierarchical cluster analysis is a multivariate statistical analysis method for classifying samples or indicators and is widely used in many scientific fields. These indicators can generate tree diagrams and can be classified into clusters with grouping algorithms and similarity measures. The indicators can also be used to calculate the density and center of each cluster from the results of cluster analysis, as well as to explain the trends in these clusters with strategic diagrams (Leal et al., 2016).

Social network analysis (SNA) is a standardized analysis method of social relations and structure. The distribution and characteristics of the relationships in the social network can be analyzed, and the structure can be displayed between the nodes (representing keywords in this study) and ties (representing the relationships of these keywords in this study; Zhang et al., 2013). The overall attributes of the network can be described concisely by resolving the SNA matrix.

There are few bibliometric analyses of CLP that apply the abovementioned methods. Mahon and Joyce (2015) created a comprehensive list of the 50 most influential papers in the field of CLP, but this research does not provide an analysis of the structure of CLP-related knowledge. For our current analysis, we aimed to provide an intuitive knowledge structure for prospective researchers from the perspective of bibliometrics and to quantitatively analyze the research characteristics and hot topics in the broad field of CLP. Here, we describe the current research interests and the historical background of CLP publications by cluster analysis based on co-citation analysis, strategy diagram of citations, and co-word analysis of keywords. We also used SNA to provide a visualized knowledge structure of CLP with its etiology, pathogenesis, clinical manifestations, and treatment.

Research Methods

Data Collection

In this study, we used the internationally recognized citation database from the Science Citation Index Expanded (SCIE) to retrieve the keywords and titles of articles with the following search terms: “cleft lip” OR “cleft palate” OR “cleft lip and palate.” The searches were conducted to differentiate publication dates from January 2000 to December 2005, from January 2006 to December 2011, and from January 2012 to December 2017. The core data set included a total of 2023, 2991, and 4026 articles, respectively, for each period. We downloaded the catalogue of all the citations of these papers and stored them in “txt” format.

Data Extraction

We applied the Bibliographic Item Co-Occurrence Matrix Builder (BICOMB; Zhao et al., 2018) to extract and count the relevant information from the data set and to construct a word matrix and a co-occurrence matrix. The BICOMB can extract the following information from related articles: period of publication, publication journal, first author, keywords, and citations. The BICOMB was supported by the China Health Policy Support Project and the upgrade to version 2.0 was funded by China Medical University.

Data Analysis

First, we determined the cutoff threshold for each time period. The high-frequency citations, keywords, and major MeSH terms/MeSH subheadings were determined by threshold value (T), which was calculated on the basis of high-frequency and low-frequency citations, keywords, and major MeSH terms/MeSH subheadings by the Donohue formula (Donohue, 1973): T = (1 + √(1 + 8i))/2, where “i” refers to the number of citations, keywords, and major MeSH terms/MeSH subheadings appearing only once.
January 2000 to December 2005: The BICOMB software was applied to extract and count the publication years, rankings among the top 20 journals, institutions, countries, regions, authors, first authors, and high-frequency cited papers ranked in the top 35. Additionally, the top 39 keywords were classified as high-frequency keywords. Then, we separately generated the term-source article matrices and co-occurrence matrices of the 35 high-frequency cited papers and 39 high-frequency keywords.

January 2006 to December 2011: We extracted the top 20 journals, institutions, countries, regions, authors, first authors, top 41 high-frequency cited papers, and top 71 high-frequency keywords. Next, we separately generated the term-source article matrices and co-occurrence matrices of high-frequency cited papers and high-frequency keywords.

January 2012 to December 2017: We extracted the top 20 journals, institutions, countries, regions, authors, first authors, top 51 high-frequency cited papers, and top 75 high-frequency keywords. We then generated the term-source article and co-occurrence matrices.

The term-source article matrices of the highly cited papers and high-frequency keywords were analyzed using the social science statistical software package (SPSS 19.0). The method of hierarchical clustering (Zhang et al., 2017) was adopted. The similarity between clusters was calculated using the Ochiai coefficient. The results of cluster analysis of these high-frequency cited papers co-citation together with high-frequency keywords were obtained.

According to the co-occurrence matrix of the highly cited papers (Nanni et al., 2013), the average publication time of each category was calculated by the publication time of each paper, which reflects the average age of the subject, called novelty. The average cited number of each category was calculated by the cited number of each paper, which reflects the level of concern, called attention degree. The citation strategic coordinates of CLP were drawn with novelty and attention degree of all categories as the horizontal axis and vertical axis, respectively. The co-occurrence matrices based on high-frequency keywords were imported into UCINET 6 software and a social network diagram was constructed.

Results

Cleft Lip and Palate-Related Article Statistics

In this study, we calculated statistics of CLP literature according to 6-year periods from 2000 to 2017. We assessed the quantity, the first author, the country/region, and the published journals of CLP-related articles. As shown in Figure 1A, in 2000, the number of CLP-related articles was 305, and the number steadily increased over the years of investigation. The number of CLP-related articles reached its maximum in 2015, with 724 articles. In 2016, it fell to 650, and, in 2017, it rose to 681.

Analysis of the statistics of the countries/regions and institutions of relevant documents (Figure 1B and C) revealed that the total number of documents in the United States far exceeded that of other countries/regions. During the 18 years of interest, the number of CLP-related articles in the United States totaled 3180, which accounted for approximately one-third of the total number of CLP articles worldwide. This reflects the United States’ leading position in this research field. Among the institutions in the United States, the University of Iowa published the most relevant documents, followed by the University of Pittsburgh, the University of San Francisco, and Harvard University.

From 2000 to 2006, only 44 articles were published in China, which was the 15th highest ranked country. However, from 2012 to 2017, the number of articles in China reached 488, representing a nearly 11-fold increase, and China’s ranking jumped to second place. In China, the Chang Gung Memorial Hospital of Taiwan was engaged in CLP research in the early days of the field. However, after 2006, the institution that published the most relevant documents in China was Sichuan University. In addition to the United States and China, the United Kingdom, Japan, and Germany comprised the top 5 countries in terms of the number of relevant publications.

Several countries, including China, demonstrated growth in the number of published CLP articles. Brazil’s number of publications grew from 69 articles from 2000 to 2006 to 231 from 2012 to 2017, representing a 3.3-fold increase. In Brazil, nearly half of the articles were written by researchers at the University of Sao Paulo. Radboud University Nijmegen in the Netherlands is another institution that contributed greatly to publications in the field of CLP, with a total of 144 articles published after 2006.

According to author statistics (Figure 1D), J. C. Murray published the most literature, with a total of 135 articles. The article he published in 2002—“Gene/environment Causes of Cleft Lip and/or Palate (Murray, 2002)—is an important review in this field: it was cited 39 times from 2000 to 2005 and 238 times from 2006 to 2017. B. Shi is a Chinese scholar who is the second most published author in the field of CLP. He published 94 papers from 2006 to 2017.

A. Heliovaara, M. Martinelli, and E. J. Leslie were the first authors with the most published papers from 2000 to 2005, from 2006 to 2011, and from 2012 to 2017 (Figure 1E), with 10 articles, 9 articles, and 12 articles, respectively. No articles by these 3 authors were identified as high-frequency citations.

The journal that published the most literature in the field was Cleft Palate-Craniofacial Journal, which is a premiere journal in the field of CLP (Figure 1F). The second most frequent journal of publication was the Journal of Craniofacial Surgery. The number of papers published by American Journal of Medical Genetics Part A, Plastic and Reconstructive Surgery, and Journal of Craniomaxillofacial Surgery was similar to each other.

High-Frequency Cited Paper Clustering and Strategic Coordinates

Using the Donohue formula and BICOMB software, we extracted the top 35 most frequently cited papers from 2000
Figure 1. (continued).
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to 2005, the top 41 papers from 2006 to 2011, and the top 51 papers from 2012 to 2017. Then, these high-frequency citations were clustered and strategically analyzed (Figure 2).

Among the high-frequency citations identified during the 18-year period of interest, papers discussing “orthodontic treatment for alveolar cleft” were consistently in the second quadrant of the strategic diagram. The “prevalence of cleft lip and palate” topic was located in the fourth quadrant for the 2000 to 2005 period and in the third quadrant for the 2006 to 2011 and 2011 to 2017 periods.

From 2000 to 2005, the topics “technique for cleft lip repair” and “TGF-β3, MSX1 genes contribute to cleft lip and palate” were in the first quadrant. Topics concerning “TTF2, P63, and IRF6 genes” were in the fourth quadrant. “Transforming growth factor-beta 3 is required for secondary palate fusion” (Proetzel et al., 1995) was the most frequently cited paper during this period.

From 2006 to 2011, “Interferon regulatory factor 6 (IRF6) gene variants and the risk of isolated cleft lip or palate” (Zucchero et al., 2004) was the most frequently cited paper. According to the strategic coordinates from this period, several topics emerged for the first time: “impaired FGF signaling” and “PVRL1 gene,” which were located in the fourth quadrant, and “TGFBR2, BMP4 gene,” which was located in the third quadrant.

From 2012 to 2017, the highest frequency citation was a review article by Dixon et al. (2011). According to the strategic coordinates, the following first-time topics emerged during this period: “genome-wide association study (GWAS),” “morphogenetic and molecular mechanisms,” and “psychosocial study of cleft lip and palate.”

**Keywords Clustering and SNA**

Using BICOMB software and constructing co-occurrence matrices, we extracted the top 39 high-frequency keywords from 2000 to 2005, top 71 keywords from 2006 to 2011, and top 75 keywords from 2012 to 2017. Then, cluster analysis and SNA analysis were performed (Figure 3). Keywords that were consistently at the center position of the SNA diagram included “craniofacial,” “submucous cleft palate,” “prenatal diagnosis,” and “psychosocial study of cleft lip and palate.”

“surgery” were newly added, with betweenness of 49.735 and 22.318, respectively. At the same time, many new nodes have been added to the edge of the network, including “polymorphism,” “Pierre Robin sequence,” “TP63,” “IRF6,” “SNP,” “p63,” and “SHH,” which represented new research topics during this period.

In the SNA diagram for the period from 2012 to 2017, the network centralization index was 29.16%. Those keywords with betweenness centrality greater than 30 were specifically marked. Newly added keywords included “polymorphism,” “velopharyngeal insufficiency,” “orofacial cleft,” “genetics,” “craniofacial,” “distraction osteogenesis,” “meta-analysis,” and “SNP.” The keyword “meta-analysis” appeared in the SNA diagram for the first time, with a betweenness of 37.095. Other new keywords were also added to the edge of the network, including “cone beam computed tomography,” “tooth agenesis,” “case-control study,” “association study,” “micrognathia,” “DiGeorge syndrome,” “NSCL/P,” “UCLP,” “GWAS,” “MTHFR,” and “CLPTM1L.”

**Discussion**

When considering the etiology of CLP, we believe that, in general, those cases without a family history may be associated with environmental risk factors; if 2 or more patients with CLP are in the same family, genetic factors are likely the primary cause of the condition (Seto-Salvia and Stanier, 2014; Kawalec et al., 2015). Environmental risk factors associated with the occurrence of CLP include the elder age of the pregnant woman, being underweight or overweight, medication history, smoking, alcohol consumption during pregnancy, folic acid deficiency, and some metabolic diseases in the pregnant woman (Stott-Miller et al., 2010; DeRoo et al., 2016; Kutbi et al., 2017).

In genetics, new technologies are increasingly used in research, and owing to these technologies, significant progress has been made in the identification of genetic and environmental causes of syndromes. In recent years, specific mutations associated with CLP have been identified using genome-wide linkage and association studies, including studies of IRF6, VAX1, MAFB, and ABCA4 genes (Beatty et al., 2010; Mangel et al., 2010; Dixon et al., 2011). However, approximately 70% of CLP cases occur as isolated entities with no other apparent cognitive or structural abnormalities; these cases are commonly termed “isolated, nonsyndromic CLP.” The cause of such CLP cases is complex. Epidemiologic, candidate gene and genome-wide studies and animal model analyses have been synthesized to gain more understanding into the causes of nonsyndromic CLP.

In this study, we chose the SCIE database for bibliometric analysis. The SCIE database is the most important literature database in the natural sciences, and it includes the most influential and important journals in more than 6000 specialties in natural science, engineering, and technology fields. In this current analysis, 9040 CLP-related articles from an 18-year period were retrieved from the SCIE database. We completed co-
citation and co-word analyses, hierarchical clustering, strategic coordinates, and SNA to analyze these articles. This is the first time that all of these methods have been used to analyze the fundamental knowledge structure of CLP.

We found that the number of published CLP articles has grown steadily since 2000, with a small peak in 2012 and a slight decline in 2013, reaching its peak in 2014 and 2015. In 2016 and 2017, the number declined slightly. This may be due to the gradual improvement in old research topics and the fact that new topics are not yet popular.

According to country/region and institution statistics, the total number of documents published in the United States consistently exceeded that of other countries/regions during the 18 years of interest. Of the total of 9040 articles, those from the United States accounted for 35.18%. These findings are likely associated with the fact that the language of the database we choose is English.

The University of Iowa, the University of Pittsburgh, the University of San Francisco, and Harvard University were the research institutions in the United States that published the most papers in the CLP field. The remaining countries ranked in the top 5 publication countries/regions were the United Kingdom, China, Japan, and Germany. This demonstrates that CLP has gained worldwide attention, likely because the global incidence of CLP is high.

The number of CLP articles increased most rapidly in China and Brazil, achieving 11-fold and 3.3-fold increases, respectively, from the first period of study (2000-2005) to the last (2012-2017). In China, the study of CLP began late but developed rapidly. Sichuan University is the research institution that has achieved the most publications in China. In Brazil, approximately half of the CLP articles were from the University of Sao Paulo.

The author who published the most articles in all 3 time periods was J. C. Murray from the Department of Pediatrics and Craniofacial Anomalies Research Center, University of Iowa. Dr Murray and his team published many important research results in the field of CLP, including genetics, genomics, and epidemiologic and exposomics tools. Additionally, Murray had 2 review articles considered high-frequency cited papers, which are highly regarded papers in the field of CLP.

Dr Shi, the second most published author, is a surgeon at the State Key Laboratory of Oral Diseases, Department of Cleft Lip and Palate Surgery, West China Hospital of Stomatology, Sichuan University. He is a well-known oral surgeon in China and has performed surgical treatments for many children with CLP. In addition, he and his team also have published many advanced research results in the pathogenesis of CLP.

Cleft Palate Craniofacial Journal published the most literature in this field, and this is the sole journal that only publishes CLP-related research. Among the other 4 journals included in the top 5 for CLP publications, 3 are orthopedic journals and 1 is a genetics journal. Of the top 5 journals, the Journal of Craniofacial Surgery is from Scotland, and the other 4 journals are from the United States.

By clustering and strategically analyzing the high-frequency cited papers of each 6-year time period, we found that the “orthodontic treatment for alveolar cleft” topic was always in the second quadrant. This demonstrates that, although this topic is not the most popular, it has received relatively stable attention. Articles on this topic have received extensive attention from orthopedic surgeons and have been published in related journals. “Prevalence of cleft lip and palate” was located in the fourth quadrant for the 2000 to 2005 period and in the third quadrant for the 2006 to 2011 and 2012 to 2017 periods, indicating that the attention of this topic has declined slightly with the appearance of new research interests.

From 2000 to 2005, the hottest research topics included “TGF-β3, MSX1” gene and “secondary bone grafting.” Highly cited papers for these topics were all published before 2000. The topic “TTF2, P63, and IRF6” genes was located in the fourth quadrant for 2000 to 2005, which indicates that these topics were new and significant advances in the field.

“FGF signaling” and “PVRL1” gene appeared as research topics for the first time in the strategic coordinates for 2006 to 2011 and were located in the fourth quadrant. This indicates that centrality was high for these topics, and the papers for these topics received much attention as soon as they were published. New topics such as “TGFBR2, BMP4, FGF10/Fgfr2b” also emerged from 2006 to 2011, and they were located in the third quadrant. The high-frequency cited papers of new topics were published after 2000.

According to the citation strategic coordinates for 2012 to 2017, we found that CLP research entered a morphogenetic and molecular mechanisms stage, and new research methods such as GWAS were introduced (Younkin et al., 2014). Moreover, the psychosocial study of CLP also began to receive attention as a new research topic, which reflects the individualized care focus of medical research.

Cluster analysis and strategic diagrams can be used to display the subject structure of the domain and estimate the maturity of each cluster, respectively. However, these 2 methods cannot calculate the central grid items and cannot reveal the relationships between the components. Social network analysis can compensate for this limitation and can be used to resolve relationships among high-frequency keywords.

In the high-frequency keywords SNA diagram for 2000 to 2005, the most central keywords included “cephalometry,” which is a term that closely relates to CLP assessment and treatment. Several other keywords are located in the center of the SNA diagram and are topics that attracted much attention during this time period: “genetics,” “speech,” “surgery,” “birth defects,” “craniofacial,” “submucous cleft palate,” “prenatal diagnosis,” and “distraction osteogenesis.”

In the SNA diagram for 2006 to 2011, the most central keywords that increased in frequency were “surgery” and “development.” At the same time, many new nodes were added to the edge of the network: “polymorphism,” “Pierre Robin sequence,” “TP63,” “IRF6,” “SNP,” “p63,” and “SHH.” This demonstrates that research on the etiology and genetics of CLP began to achieve notable results during this period.

In the SNA diagram for 2012 to 2017, more keywords were located in the center than in the previous time periods. These included “polymorphism,” “velopharyngeal insufficiency,”
“orofacial cleft,” “genetics,” “craniofacial,” “distraction osteogenesis,” and “meta-analysis.” This demonstrates that the field of CLP achieved stable research content. Among these keywords, “meta-analysis” appeared for the first time in the SNA diagram, and the betweenness reached 37.095. This indicates that the number of meta-analysis articles in the field of CLP rapidly increased during this period, and it has become a new favored research area (Feng et al., 2014). Moreover, many new keywords were added to the edge of the network, such as “cone beam computed tomography,” “tooth agenesis,” “case-control study,” “association study,” “micrognathia,” “DiGeorge syndrome,” “NSCL/P,” “UCLP,” “GWAS,” “MTHFR,” and “CLPTM1L,” which represent new research content.

Conclusion
We conducted a bibliometric analysis of CLP-related research topics during 6-year periods from 2000 to 2017. Cleft lip and palate is a common congenital malformation, and literature related to this condition steadily increased in the early 21st century. Recently, the subject has become more stable.

Our research included clustering analysis of highly cited papers and keywords and then strategic diagram analysis of highly cited papers and SNA of high-frequency keywords. Citation analysis reflects the research foundation of CLP, while keyword clustering and SNA reflect some of the current hot topics in CLP research. Therefore, our research can provide some clues for selecting future research topics.

There are some limitations to our study that must be considered. First, the literature downloaded from SCIE does not include all published literature, so it may affect the results of the analysis. Second, high-frequency keyword co-occurrence analysis is based on the intercept frequency, so new, very low-frequency keywords may be ignored. Furthermore, depending on the keywords alone, some information may be lost. In the future, we will search a variety of databases and combine more analytical tools, such as other co-word analysis methods and different MeSH terms, to further improve the research results and identify trends in CLP research.

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