

Trends in Research Related to Keratoconus From 2009 to 2018: A Bibliometric and Knowledge Mapping Analysis

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Purpose: To map the publication trends in and explore hotspots of keratoconus research.

Methods: A bibliometric analysis based on the Web of Science Core Collection was conducted to investigate the publication trends in research related to keratoconus. The records extracted were analyzed, and a knowledge map was constructed using VOSviewer v.1.6.10 to visualize the annual publication number, distribution of countries, international collaborations, author productivity, source journals, intellectual base, and research hotspots in the field of keratoconus.

Results: In total, 3194 peer-reviewed publications on keratoconus published between 2009 and 2018 were retrieved, and the annual research output increased with time. The United States ranked the highest among the countries with the most publications, and Tehran University of Medical Sciences was the most active institution. JL Alio contributed to the most number of publications on keratoconus, and *Cornea* was the most prolific journal publishing keratoconus research. The top cited references mainly focused on corneal collagen cross-linking. The keywords formed 6 clusters: 1) pathogenesis of keratoconus, 2) corneal collagen cross-linking, 3) management for early-stage keratoconus, 4) corneal parameter

measurement, 5) surgical treatment of keratoconus, and 6) corneal biomechanics-related research.

Conclusions: On the basis of the data extracted from the Web of Science Core Collection, the quantity and quality of publications on keratoconus were assessed using bibliometric techniques. The cited references and research hotspots could provide insights into keratoconus research as well as valuable information to cornea specialists for performing research in this field and discovering potential collaborators.

Key Words: keratoconus, bibliometric analysis, mapping knowledge domain, VOSviewer

(*Cornea* 2019;38:847–854)

Keratoconus is a progressive corneal ectasia characterized by thinning and weakening of the cornea that leads to irregular astigmatism, refractive myopia, and decreased vision due to corneal scarring and cone-like appearance of the cornea.¹ Academic journals have published numerous articles on keratoconus-related research in past decades. In the present study, bibliometric analysis and mapping knowledge domain (MKD) methods were applied to explore the status of keratoconus research.

Bibliometric analysis is a type of document analysis method used to analyze the related literature using mathematical and statistical methods. It allows quantitative measurement of the distributions of profiles, as well as the relationships and clusters of studies.² MKD is a method used to visually present the knowledge structure by means of scientific measurement and graphic plotting. Using databases and visualization tools (CiteSpace and VOSviewer), MKD provides a novel way to conduct literature mining and reveal the core structure of scientific knowledge.³

Assessing research trends in an academic field is important for researchers to identify research gaps that future studies should focus on. Recently, co-citation analyses and keyword co-occurrence analyses have been exploited for knowledge mapping.⁴ The aim of our study was to perform a comprehensive analysis of studies on keratoconus. Specifically, this study assessed the increase in the number of publications, international collaborations, author productivity, and source journals, and performed co-citation analysis and keyword co-occurrence analysis related to keratoconus research. This short summary of the topic clusters could reveal the research development status and provide some hints to cornea specialists performing research in this field.

Received for publication November 19, 2018; revision received March 15, 2019; accepted March 20, 2019. Published online ahead of print April 25, 2019.

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The work was supported by Basic Research Fund for Young Instructors of Higher Education in Liaoning Province (Grant No. LQNK201717). Shenyang Science and Technology Plan Projects (Grant No. 18-014-4-46).

The authors have no conflicts of interest to disclose.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.corneajrnl.com).

Ethics approval and consent to participate: This study did not meet criteria for human or animal subject research; no formal ethics approval and consent were required in the present study.

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MATERIALS AND METHODS

Data Source and Research Process

The Science Citation Index Expanded database in the Web of Science Core Collection (WoSCC) was retrieved online as the data source for this study. The retrieval topic was “keratoconus,” the timespan was “from 2009 to 2018,” and the document type was “article.” No language restrictions were set. The retrieved results were saved as “Plain text” with “full record and cited references.” Raw data from the WoSCC were initially downloaded. The authors F.Z. and J.X. went through the process of data extraction and verified any data loss or duplicate data entry due to human error. The following basic information regarding each article was collected: author, title, abstract, institution, country, journal, keywords, and references.

Analytical Tool and Method

Visualization software can produce node-link maps that allow us to intuitively observe the publication outputs, hotspots, and other aspects of a research field. In this study, the data were imported into VOSviewer v.1.6.10 and analyzed systematically. VOSviewer (www.vosviewer.com), developed by van Eck and Waltman,⁵ is a literature visualization software that has advantages of displaying cluster analysis results. The manual for VOSviewer is available online (http://www.vosviewer.com/documentation/Manual_VOSviewer_1.6.10.pdf). In the knowledge maps generated using VOSviewer, items are represented as nodes and links. The nodes and their labels, such as countries, organizations, authors, co-citation literature, and keywords, are proportional to the weight of the analysis components. The links between the nodes reflect the relationship between the components. CiteSpace IV (Drexel University, Philadelphia, PA) was used to capture keywords with strong citation bursts, which could be considered as predictors of research frontiers.

In this study, co-citation cited reference and keyword co-occurrence networks were applied to construct the knowledge map of keratoconus research. The clustering of similar references resulted in co-citation cited reference clusters, which could be used to explore the main topics in the intellectual base. Keywords are used to express the theme of the academic documents, and the clustering analysis of these co-occurrence keywords can reveal the knowledge structure and hotspots in this research field.

RESULTS

Yearly Quantitative Distribution of Publications

On the basis of the selection criteria, we identified and included 3194 publications on keratoconus that were indexed in the WoSCC from 2009 to 2018. The number of publications showed a gradually increasing trend over time, increasing from 207 in 2009 to 343 in 2018 (Fig. 1A). Through keyword burst detection analysis (Fig. 1B), we detected 36 keywords that represented citation bursts; among

these, “ultraviolet-A” and “cross-linking” showed citation bursts from 2013 and 2014, respectively.

Distribution of Productive Countries in Keratoconus Research

According to the retrieved results, the 3194 publications originated from 82 countries. Table 1 lists the top 10 countries engaged in keratoconus research, with 2676 articles accounting for 83.78% of the total number of publications. The United States contributed the most publications (681, 21.32%), followed by China (277, 8.67%) and Germany (268, 8.39%). Citation analysis according to countries showed that the United States had 11,715 citations, followed by Italy (4496 citations) and Germany (3995 citations).

In VOSviewer, citation analysis was used to generate the knowledge domain map of the main countries involved in keratoconus research. Supplemental Figure 1 (see Supplemental Digital Content 1, <http://links.lww.com/ICO/A792>) is a density heat map that displays the distribution of productive countries in keratoconus research. The color of the area corresponds to the number of articles published by that country. The greater the number of publications, the warmer the color, and the smaller the number, the cooler the color.

Quantitative Analysis of Research Organizations

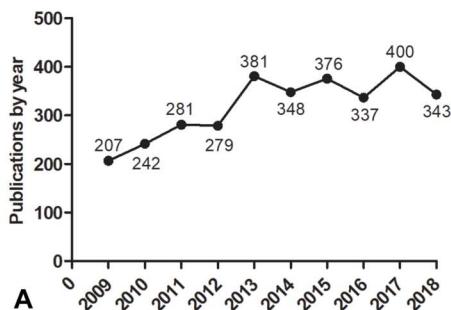
According to the retrieved results, the 3194 publications originated from 2594 organizations. The top 10 organizations with the greatest output in this research field published 509 articles, accounting for 15.94% of the publications (Table 2).

In VOSviewer, co-authorship analysis was adopted to generate the knowledge domain map of the main research organizations in order to demonstrate the collaboration network among the research organizations involved in keratoconus research. In Supplemental Figure 2 (see Supplemental Digital Content 2, <http://links.lww.com/ICO/A793>), each node represents an organization, and the node size indicates the number of publications. The links between the nodes represent the collaborations. The greater the link strength, the closer the collaboration.

Distribution of Authors and Co-authorship Analysis of Research Groups

According to the retrieved results, over 8003 authors contributed to keratoconus research. Among the top 10 authors, Alio JL (57 publications) ranked the first, followed by Seitz B (56 publications) and Shetty R (54 publications), indicating their productive contribution to keratoconus research. The information regarding author co-citations was also analyzed. Among the top 10 co-cited authors, Wollensak G (2540 co-citations) ranked the first, followed by Rabino-witz YS (1378 co-citations) and Spoerl E (979 co-citations), indicating their important roles and strong influence in keratoconus research (Table 3).

In VOSviewer, co-authorship analysis was applied to generate the knowledge domain maps of the main research



Top 36 Keywords with the Strongest Citation Bursts

| Keywords | Year | Strength | Begin | End | 2009 - 2018 |
|-------------------------------------|------|----------|-------|------|-------------|
| descemet's membrane | 2009 | 15.4818 | 2009 | 2012 | |
| term follow up | 2009 | 14.7041 | 2009 | 2012 | |
| deep anterior lamellar keratoplasty | 2009 | 12.0671 | 2009 | 2011 | |
| big bubble technique | 2009 | 10.9511 | 2009 | 2011 | |
| keratectasia | 2009 | 10.1571 | 2009 | 2010 | |
| apoptosis | 2009 | 9.221 | 2009 | 2011 | |
| higher order aberration | 2009 | 8.6916 | 2009 | 2012 | |
| orientation | 2009 | 7.0548 | 2009 | 2010 | |
| contact len | 2009 | 6.6296 | 2009 | 2013 | |
| complication | 2009 | 6.2734 | 2009 | 2010 | |
| orbscan ii | 2009 | 4.8612 | 2009 | 2013 | |
| surgery | 2009 | 2.896 | 2009 | 2010 | |
| myopia | 2009 | 2.8033 | 2009 | 2010 | |
| transplantation | 2009 | 10.7935 | 2010 | 2011 | |
| intac | 2009 | 9.9202 | 2010 | 2012 | |
| videokeratography | 2009 | 11.2227 | 2011 | 2013 | |
| corneal topography | 2009 | 6.8986 | 2012 | 2013 | |
| uva | 2009 | 6.2374 | 2013 | 2014 | |
| forme fruste keratoconus | 2009 | 8.8302 | 2014 | 2015 | |
| epithelium | 2009 | 8.134 | 2014 | 2015 | |
| cross linking | 2009 | 7.8495 | 2014 | 2018 | |
| ultraviolet | 2009 | 6.9904 | 2014 | 2015 | |
| light | 2009 | 6.6683 | 2014 | 2016 | |
| cross-linking | 2009 | 5.616 | 2014 | 2015 | |
| severity | 2009 | 9.9303 | 2015 | 2016 | |
| anterior lamellar keratoplasty | 2009 | 9.1103 | 2015 | 2016 | |
| subclinical keratoconus | 2009 | 7.6621 | 2015 | 2018 | |
| corneal cross-linking | 2009 | 7.6621 | 2015 | 2018 | |
| optical coherence tomography | 2009 | 5.063 | 2015 | 2018 | |
| efficacy | 2009 | 12.3886 | 2016 | 2018 | |
| children | 2009 | 10.7953 | 2016 | 2018 | |
| corneal | 2009 | 8.5284 | 2016 | 2018 | |
| tissue | 2009 | 6.2027 | 2016 | 2018 | |
| parameter | 2009 | 5.9745 | 2016 | 2018 | |
| microscopy | 2009 | 5.7709 | 2016 | 2018 | |
| follow up | 2009 | 4.6285 | 2016 | 2018 | |

FIGURE 1. The annual number of publications in keratoconus study from 2009 to 2018 (A), Top 36 keywords with the strongest citation bursts on keratoconus from 2009 to 2018 (B).

groups. As shown in Supplemental Figure 3 (Supplemental Digital Content 3, <http://links.lww.com/ICO/A794>), each node represents an author, and the node size corresponds to the number of publications. The links connecting 2 nodes represent the cooperative relationship between 2 authors, and the thickness of the links represents the intensity of cooperation.

Quantitative Analysis of Source Journals

The retrieved results indicated that 273 journals published articles on keratoconus research. The top 10 active journals are presented in Table 4. *Cornea* published the highest number of articles (472, 14.78%), followed by the *Journal of Cataract and Refractive Surgery* (280, 8.77%) and the *Journal of Refractive Surgery* (254, 7.95%). Articles

TABLE 1. Top 10 Productive Countries in Keratoconus Study, 2009 to 2018

| Rank | Country | Count | Percentage | Citation |
|------|---------------|-------|------------|----------|
| 1 | United States | 681 | 21.32 | 11,715 |
| 2 | China | 277 | 8.67 | 2136 |
| 3 | Germany | 268 | 8.39 | 3995 |
| 4 | Turkey | 257 | 8.05 | 2357 |
| 5 | England | 239 | 7.48 | 3845 |
| 6 | Spain | 233 | 7.29 | 3046 |
| 7 | Italy | 204 | 6.39 | 4496 |
| 8 | India | 191 | 5.98 | 2317 |
| 9 | Brazil | 179 | 5.60 | 2120 |
| 10 | Iran | 147 | 4.60 | 1174 |

published in these 3 journals accounted for 31.5% of all publications included in this study.

Reference Co-citation Analysis: Knowledge Bases of Keratoconus Research

Through co-citation analysis of the cited references, the intellectual base of a research field can be constituted efficiently. The top 10 co-cited references are presented in Table 5, and the cited references classified according to clusters are presented in the Supplemental Digital Content 4 (see Supplemental Dataset, <http://links.lww.com/ICO/A795>).

In VOSviewer, co-citation analysis was applied to generate the network of co-cited references on keratoconus research. The minimum citation number of a cited reference was set as 20. Of the 31,280 cited references, 694 co-cited references met the threshold. On the basis of this network, the references with similarities were clustered, and the 5 main clusters were denoted using the colors red, green, blue, yellow, and purple (see Supplemental Figure 4, Supplemental Digital Content 5, <http://links.lww.com/ICO/A796>).

TABLE 2. Top 10 Productive Organizations in Keratoconus Study, 2009 to 2018

| Rank | Organization | Country | Count | Percentage |
|------|--|---------------|-------|------------|
| 1 | Tehran University of Medical Sciences | Iran | 69 | 2.16 |
| 2 | Federal University of São Paulo | Brazil | 68 | 2.13 |
| 3 | University of Crete | Greek | 56 | 1.75 |
| 4 | The University of Melbourne | Australia | 51 | 1.60 |
| 5 | University of Alicante | Spain | 47 | 1.47 |
| 6 | Miguel Hernández University | Spain | 47 | 1.47 |
| 7 | The Chinese University of Hong Kong | China | 45 | 1.41 |
| 8 | The University of Auckland | New Zealand | 45 | 1.41 |
| 9 | Shahid Beheshti University of Medical Sciences | Iran | 43 | 1.35 |
| 10 | University of Miami | United States | 38 | 1.19 |

TABLE 3. Top 10 Productive Authors and Co-cited Authors in Keratoconus Study, 2009 to 2018

| Rank | Author | Count | Co-cited Author | Count |
|------|----------------|-------|------------------|-------|
| 1 | Alio JL | 57 | Wollensak G | 2540 |
| 2 | Seitz B | 56 | Rabinowitz YS | 1378 |
| 3 | Shetty R | 54 | Spoerl E | 979 |
| 4 | Kymionis GD | 52 | Kymionis GD | 858 |
| 5 | Ambrosio R | 45 | Kanellopoulos AJ | 677 |
| 6 | Hafezi F | 45 | Caporossi A | 612 |
| 7 | Jhanji V | 41 | Mazzotta C | 583 |
| 8 | Piñero DP | 41 | Alio JL | 568 |
| 9 | Langenbucher A | 36 | Vinciguerra P | 509 |
| 10 | McGhee CNJ | 36 | Piñero DP | 449 |

Keyword Co-occurrence Analysis: Topics of Keratoconus Research

Analysis of high-frequency keywords can be used to determine the important topics in an academic domain. In VOSviewer, co-occurrence analysis was applied to generate the keyword co-occurrence network of keratoconus research. The minimum co-occurrence number of a keyword was set as 10. Of the 6251 extracted keywords used in keratoconus research, 471 keywords met the threshold. On the basis of the network, the keywords with similarities were clustered, and the 6 main clusters were denoted using the colors red, green, blue, yellow, purple, and pink (see Supplemental Figure 5, Supplemental Digital Content 6, <http://links.lww.com/ICO/A797>).

DISCUSSION

The variation in the number of academic publications is an important research index, which can reflect the

TABLE 4. Top 10 Source Journals in Keratoconus Study, 2009 to 2018

| Rank | Journal Title | Country | Count | Percentage |
|------|---|---------------|-------|------------|
| 1 | <i>Cornea</i> | United States | 472 | 14.78 |
| 2 | <i>Journal of Cataract and Refractive Surgery</i> | United States | 280 | 8.77 |
| 3 | <i>Journal of Refractive Surgery</i> | United States | 254 | 7.95 |
| 4 | <i>Investigative Ophthalmology and Visual Science</i> | United States | 163 | 5.10 |
| 5 | <i>American Journal of Ophthalmology</i> | United States | 115 | 3.60 |
| 6 | <i>Contact Lens and Anterior Eye</i> | Netherlands | 97 | 3.04 |
| 7 | <i>British Journal of Ophthalmology</i> | England | 79 | 2.47 |
| 8 | <i>Journal of Ophthalmology</i> | United States | 77 | 2.41 |
| 9 | <i>Eye & Contact Lens-science and Clinical Practice</i> | United States | 71 | 2.22 |
| 10 | <i>European Journal of Ophthalmology</i> | Italy | 62 | 1.94 |

TABLE 5. Top 10 Co-cited References in Keratoconus Research, 2009 to 2018

| Rank | Co-cited Reference | Title | Count | Cluster |
|------|--|--|-------|---------|
| 1 | Rabinowitz YS. <i>Surv Ophthalmol.</i> 1998;42:297 | Keratoconus | 851 | 3 |
| 2 | Wollensak G. <i>Am J Ophthalmol.</i> 2003;135:620 | Riboflavin/UV-A-induced collagen crosslinking for the treatment of keratoconus | 797 | 2 |
| 3 | Raiskup-wolf F. <i>J Cataract Refr Surg.</i> 2008;34:796 | Collagen crosslinking with riboflavin and UV-A light in keratoconus: long-term results | 363 | 2 |
| 4 | Krachmer JH. <i>Surv Ophthalmol.</i> 1984;28:293 | Keratoconus and related noninflammatory corneal thinning disorders | 338 | 3 |
| 5 | Wollensak G. <i>J Cataract Refr Surg.</i> 2003;29:1780 | Stress-strain measurements of human and porcine corneas after riboflavin-UV-A-induced cross-linking | 322 | 2 |
| 6 | Spoerl E. <i>Cornea.</i> 2007;26:385 | Safety of UV-A-riboflavin cross-linking of the cornea | 272 | 2 |
| 7 | Spoerl E. <i>Exp Eye Res.</i> 1998;66:97 | Induction of cross-links in corneal tissue | 268 | 2 |
| 8 | Caporossi A. <i>Am J Ophthalmol.</i> 2010;149:585 | Long-term results of riboflavin UV-A corneal collage cross-linking for keratoconus in Italy: the Siena eye cross study | 243 | 2 |
| 9 | Wollensak G. <i>Curr Opin Ophthalmol.</i> 2006;17:356 | Crosslinking treatment of progressive keratoconus: new hope | 229 | 2 |
| 10 | Kennedy RH. <i>Am J Ophthalmol.</i> 1986;101:267 | A 48-year clinical and epidemiologic study of keratoconus | 199 | 3 |

UV-A, ultraviolet-A.

development trend in a field. As shown in Figure 1A, 3194 publications on keratoconus published from 2009 to 2018 were retrieved, and the annual research output generally increased with time. Burst keywords are considered indicators of research frontiers or emerging trends. The top 36 keywords with the strongest citation bursts are shown in Figure 1B. The keyword “cross-linking” showed a citation burst from 2014. With the emergence of the corneal collagen cross-linking (CXL) method in keratoconus treatment, many research projects revolved around this topic. In accordance with the line chart, the number of papers increased from 279 to 381 in 2013.

In the analysis of the most productive countries shown in Table 1, the United States accounted for 21.32% of publications and ranked the highest in citation numbers. This indicates that the United States is the international scientific center in keratoconus research.

The analysis of the distribution of research organizations revealed the most productive organizations and collaborations within the groups in a research field. As shown in Table 2, the most productive research institutions were Tehran University of Medical Sciences (69 publications) and the Federal University of São Paulo (68 publications). In terms of the number of links, the Federal University of São Paulo presented the highest number (17 links), which indicated that this organization is the key node in the collaboration network (see Supplemental Figure 2, Supplemental Digital Content 2, <http://links.lww.com/ICO/A793>). The United States had the highest output of publications in most fields of ophthalmology. However, geographical distribution may contribute to the prevalence rates of diseases, thereby leading to different research priorities in different countries. Keratoconus showed a high prevalence in countries with a warm climate, such as Middle Eastern and Asian countries, and a low prevalence in countries with a cold climate, such as North American countries, Russia, and the United Kingdom. Oxidative stress caused by ultraviolet exposure is a risk factor in the development of keratoconus.⁶ Nevertheless, countries like Australia and New Zealand presented higher than expected productivity. Moreover, they are increasing their relative productivity at a greater rate than are North American countries.⁷ These probably could be the reasons why the most productive country is the United States and the most productive research organization is located in Iran.

Constructing the knowledge map of the co-authorship network can provide valuable information to individual researchers seeking collaboration opportunities. The co-authorship groups are shown in Supplemental Figure 3 (Supplemental Digital Content 3, <http://links.lww.com/ICO/A794>). The first (red-colored) group has Prof. Hafezi F as the core; the second (green-colored) group has Prof. Jhanji V as the core; the third (blue-colored) group has Prof. Seitz B as the core; the fourth (yellow-colored) group has Prof. Shetty R as the core; the fifth (purple-colored) group has Prof. Touboul D as the core; the sixth (grey-colored) group has Prof. Kymionis GD as the core; and the seventh (orange-colored) group has Prof. Alio JL as the core.

A distribution analysis of academic journals helps determine the core journals in a certain field. To this end, *Cornea*, which has published the highest number of articles on keratoconus, is the most prolific journal publishing keratoconus research.

On the basis of the premise that high-quality research will be extensively cited, citation parameters were used to describe related topics within the selected articles.⁸ Through co-citation analysis, a large number of cited references can effectively show the background of the study. Therefore, we conducted cluster analysis to explore the main topics of keratoconus research. As shown in Supplemental Figure 4 (Supplemental Digital Content 5, <http://links.lww.com/ICO/A796>), the cited references were divided into 5 clusters, and the concentrated connections between the clusters indicated that the topics in the knowledge background were centralized. Cluster #1 (red-colored) mainly presented the risk factors of ectasia occurrence after refractive surgery, including the biomechanical

properties of the cornea and corneal thickness measurement. Cluster #2 (green-colored) mainly focused on CXL research. As shown in Table 5, the top 10 co-cited high-frequency references in keratoconus research mainly focused on this field. A publication with the title “Riboflavin/ultraviolet-A-induced collagen crosslinking for the treatment of keratoconus” ranked second in both frequency count and link weight. Cluster #3 (blue-colored) mainly focused on the genetics and epidemiology of keratoconus. With respect to the parameters of frequency count and link weight, publications with the title “Keratoconus” and “Keratoconus and related noninflammatory corneal thinning disorders” ranked the first and fourth, respectively. Cluster #4 (yellow-colored) and Cluster #5 (purple-colored) mainly presented the management of the early or late stage of keratoconus.

Keyword co-occurrence analysis is a common bibliometric research method because the assigned keywords are considered to represent the search theme. Thus, the internal structure of the related literature and the frontier discipline can be revealed. As shown in Supplemental Figure 5 (Supplemental Digital Content 6, <http://links.lww.com/ICO/A797>), the topics of keratoconus mainly formed 6 clusters, and the keywords in the same cluster showed greater similarity to a specific research topic. With reference to the characteristics and status of keratoconus research, the following 6 clusters were analyzed.

Cluster #1 (red) represents keywords related to the pathogenesis of keratoconus. The extracted co-occurrence keywords included “expression,” “apoptosis,” “oxidative stress,” “mutations,” “gene,” and “inflammatory molecules.” At present, the oxidative stress induced by ultraviolet radiation and genetic mutations play important roles in the pathogenesis of keratoconus.⁹ Compared with the normal cornea, the corneas of patients with keratoconus showed increased generation of reactive oxygen species owing to oxidative stress.¹⁰ Increased reactive oxygen species generation owing to oxidative stress and decreased antioxidant expression in the keratoconus cornea may accelerate keratocyte apoptosis, eventually leading to thinning and deformation of the keratoconus cornea.¹¹ Several studies have reported that multiple genes, proteinases, and inflammatory mediators are associated with keratoconus. Various genetic susceptibility loci and pathways are associated with central corneal thickness (CCT). Li et al¹² demonstrated that the CCT-associated gene *COL5A1* contributes to normal variation in CCT and is associated with clinical corneal thinning in keratoconus. Lu et al¹³ showed that *FOXO1* and *FNDC3B* conferred relatively large risks for keratoconus and that the collagen and extracellular matrix pathways are involved in the regulation of CCT. Keratoconus is defined as a degenerative noninflammatory corneal disorder; however, various studies have identified altered cytokine (interleukin [IL]-1, IL-6, tumor necrosis factor- α , IL-17, and transforming growth factor- β 2) and immune mediator levels in patients with keratoconus.¹

Cluster #2 (green) represents keywords related to corneal CXL, such as “riboflavin,” “progressive keratoconus,” “ultraviolet-A,” “collagen cross-linking,” “stroma,” and

“keratectasia.” The primary indications for corneal CXL are progressive keratoconus in adults and post-laser in situ keratomileusis (LASIK) ectasia.¹⁴ Corneal CXL is a novel invasive method for modifying the stromal structure of the cornea by increasing the formation of chemical bonds among collagen fibrils.¹⁵ Wollensak¹⁶ first reported the clinical study on the riboflavin-ultraviolet-A-induced corneal CXL procedure for the treatment of progressive keratoconus in adults. To analyze the long-term outcome of corneal CXL for progressive keratoconus, Raiskup et al¹⁷ compared the mean apical keratometry value, the mean maximum K/minimum K values, and the corrected distance visual acuity after a 10-year follow-up of patients undergoing corneal CXL. Recent studies have shown that the standard epithelium-off (Dresden) protocol can effectively inhibit the progression of keratoconus. However, this protocol requires a minimum corneal thickness of 400 μm .¹⁸ The epithelium-on protocol is a modified technique that is completed without epithelial debridement, but evaluations of its efficacy have yielded inconsistent results.¹⁴ The emerging combination of corneal CXL with refractive procedures (termed CXL plus) optimizes the visual outcome but requires further investigation and long-term efficacy studies.¹⁹ As corneal CXL has the capacity to halt the ectatic process and to improve visual outcomes, we envisage that CXL will continue to play an increasingly prominent role in the management of patients with ectasia.

Cluster #3 (blue) represents corneal parameter measurements, such as “LASIK,” “ectasia,” “corneal topography,” “optical coherence tomography (OCT),” “Pentacam,” “refractive surgery,” “subclinical keratoconus,” “forme fruste keratoconus,” “ultrasound pachymetry,” “corneal thickness,” “diagnosis,” and “iatrogenic keratoconus.” The use of laser refractive surgery has increased significantly in recent years, and this makes corneal anomaly detection very important.²⁰ Risk factors for refractive surgery include keratoconus, high myopia, low residual stromal bed thickness caused by excessive ablation or thick flap creation, and forme fruste keratoconus.²¹ Therefore, an accurate assessment of the corneal status and diagnosis of clinical or subclinical keratoconus is of great importance. Corneal topography and ultrasound pachymetry are the main detection tools for keratoconus. However, for incipient and subclinical keratoconus, traditional detection methods are considered inadequate. New technologies, including OCT and Pentacam, that help detect potential topographic abnormalities make it possible to identify high-risk patients. Li et al²² reported that Fourier-domain OCT could map corneal epithelial and stromal thickness changes and could thus be useful in detecting early keratoconus. Huseynli et al²³ reported that the parameters derived from Pentacam can effectively differentiate subclinical and clinical keratoconus from non-keratoconic eyes with thin corneas. Iatrogenic ectasia is considered one of the most common complications after LASIK. When corneal ectasia occurs, various treatments, including corneal CXL, rigid gas permeable contact lenses, intrastromal corneal ring segment (ICRS) implantation, and intraocular pressure (IOP) reduction, may be applied before corneal transplantation.²⁴

Cluster #4 (yellow) represents keywords related to the management of early-stage keratoconus such as “management,” “ICRS,” “femtosecond laser,” “astigmatism,” “photo-refractive keratectomy (PRK),” “higher-order aberrations,” “corneal ectasia,” and “contact lens.” The management of keratoconus depends on the progress and stage of the disease. Various contact lenses, such as the rigid gas permeable contact lens, soft toric lens, piggy-back contact lens, and scleral lens, can help gain improved vision and correct irregular astigmatism.²⁵ In keratoconus, ICRS implantation reduces corneal distortion by flattening the steep area of the cornea and reshaping it.¹⁵ As for the insertion method of the ICRS, the canal can be created mechanically or with a femtosecond laser. Piñero et al²⁶ reported that higher order, spherical, and coma-like aberrations were significantly lowered when using the femtosecond laser-assisted method instead of the mechanical method. For the treatment of corneal ectasia, topography-guided or wavefront-guided PRK may help reduce irregular astigmatism in mild to moderate keratoconus and improve the corrected distance visual acuity.²⁷ Combining corneal CXL with keratorefractive procedures, such as ICRS implantation, PRK, and phakic intraocular lens implantation, is an effective method to improve visual acuity and may even reduce the need for invasive surgeries.²⁸

Cluster #5 (purple) represents surgical treatments for keratoconus, such as “penetrating keratoplasty (PKP),” “deep anterior lamellar keratoplasty (DALK),” “corneal transplantation,” and “the big-bubble technique.” Specialized contact lenses can offer relief to some patients with keratoconus having visual impairments, and some patients may adopt riboflavin-ultraviolet-A-induced corneal CXL treatment.²⁹ However, 10% to 20% of patients may still need corneal transplantation.³⁰ For such patients, PKP or DALK is used depending on the extent of corneal scarring. During DALK, the endothelium and Descemet membrane are separated from the corneal stroma through intrastromal air injection (big-bubble technique).³¹ Yüksel et al³² reported that big-bubble DALK results in earlier visual improvement than does PKP. However, at 1 year, the visual and topographic results are similar to those of PKP. Postoperative complications such as graft rejection and elevated IOP are more frequent in PKP. Therefore, big-bubble DALK is a safer alternative surgical method for patients with keratoconus.

Cluster #6 (pink) represents corneal biomechanics-related research, such as “ocular response analyzer,” “biomechanical properties,” “IOP,” “biomechanics,” “CCT,” and “corneal hysteresis.” Changes in corneal biomechanical properties in keratoconus are postulated to occur before the disease becomes topographically apparent. Corneal biomechanical properties, which are characterized by corneal hysteresis and the corneal resistance factors, provide new indicators for the diagnosis of keratoconus.³³ These changes occur because of abnormalities in stromal collagen and extracellular matrix as a result of the disease process.³⁴

This bibliometric and MKD analysis of keratoconus research could depict the research output and knowledge structure over the past decade to some extent. However, the results of our analysis are affected by some methodological

limitations that should be considered. First, only publications from 2009 to 2018 were extracted from the WoSCC, and these may not sufficiently represent all of the topics in keratoconus research. Because the database is being continuously updated, analyses of new emerging topics should be conducted in the future. Second, the primary data used for analysis were extracted from the WoSCC, which is a database more suited for performing advanced citation analysis. Thus, our analysis was performed using data solely extracted from the WoSCC and did not include data extracted using other search engines, such as PubMed, Scopus, or Google Scholar. Third, a linguistic bias may exist because most publications in the WoSCC were in English.

ACKNOWLEDGMENTS

The authors would like to thank all reviewers for their valuable comments.

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