



Bibliometric analysis of scientific publications on cryptorchidism: Research hotspots and trends between 2000 and 2022

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ABSTRACT

Background: Cryptorchidism is defined as failure of unilateral or bilateral testicular descent, which increases the risk of infertility and testicular carcinoma. Although there is much research on cryptorchidism, few studies have used the bibliometric analysis method. The purpose of this study was to conduct a comprehensive analysis of cryptorchidism from multi-dimensional perspectives to summarize the research hotspots and trends in cryptorchidism research.

Methods: Relevant studies on cryptorchidism were retrieved from the Web of Science Core Collection (WoSCC) database from 2000 to 2022. A comprehensive bibliometric analysis of cryptorchidism was performed by using the CiteSpace, Tableau Public, and VOSviewer software, including the annual distributions of publications, countries, authors, institutions, journals, references, and keywords.

Results: From January 1st, 2000 to May 17th, 2022, a total of 5023 papers concerning cryptorchidism were identified for analysis. The USA contributed the most publications ($n = 1193$) in this field, and the annual number of publications rose rapidly in China. The University of Melbourne published the largest number of papers ($n = 131$). "Hutson, John M." was the most core author ranked by publications ($n = 51$), and "Skakkebaek, Niels E." enjoyed the largest number of citations (4441). The *JOURNAL OF UROLOGY* published the largest number of papers ($n = 225$), while the average citations per publication of the 75 papers in *HUMAN REPRODUCTION* reached 62.38. Additionally, burstness analysis of references and keywords showed that cryptorchidism research was mainly focused on the exploration of the optimal mode of treatment for cryptorchidism, including hypogonadism such as Kallmann syndrome and Klinefelter syndrome.

Conclusion: Cryptorchidism has attracted continuous attention from the scientific community concerned. International collaboration in the field has witnessed significant growth in recent years and remains essential to further enhance collaborative efforts between scholars from different countries. In addition, the exploration of the optimal treatment modality for cryptorchidism, especially in the prevention of adult infertility, remains a major focus of future research. High-quality follow-up studies are also needed in the future. The pathogenesis (especially at the genetic level) and treatment of hypogonadism such as Kallmann syndrome and Klinefelter syndrome have attracted increasing attention recently, which may usher in some breakthroughs in coming years.

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1. Introduction

Cryptorchidism, also called undescended testis, refers to the failure of the unilateral or bilateral testes to completely descend into the scrotum during fetal development, which is one of the most common congenital anomalies in the genitourinary system. The incidence of cryptorchidism is 2–9% in newborns [1]. The exact etiology of undescended testis remains unclear at present, although most researchers believe that it is attributed to both endogenous and exogenous risk factors. Exposure to endocrine-disrupting chemicals, maternal smoking, gestational diabetes, and intrauterine exposure to analgesics are supposed to increase the risk of cryptorchidism. Impairment to INSL3/RXFP2 signaling pathway can affect the normal migration of the testis into the scrotum [2–4]. Persistent or untreated cryptorchidism could impair the male reproductive function, depending on the number of spermatogonia and maturation arrests involved. In addition, the risk of developing testicular cancer in men with a history of cryptorchidism is 3.7–7.5 fold as high as that in men without a history of cryptorchidism [5]. The optimal operation time of orchidopexy is proposed to be at the age of six months when the testis is found to be less likely to descend into the scrotum spontaneously, knowing that timely surgery can also improve the long-term semen quality [6,7]. However, the application of hormones should be prudent in the management of cryptorchidism [8,9]. As there is a yearly rapid increase in the number of publications concerning cryptorchidism, analysis of such a large army of medical literature by traditional ways is a formidable challenge, so quick and effective novel methods for literature analysis are urgently required.

Bibliometric analysis is a quantitative statistical method of the scientific literature that can analyze and describe the dynamic changes and research progresses in certain specific research fields [10]. With the help of some visualization tools including CiteSpace and VOSviewer software, such quantitative results could be presented with visual knowledge maps. According to the textual data and publications available, it is conducive to exploring the distribution of the literature, current research situation, shifting of research hotspots, and possible research trends. Currently, no systematic bibliometric analysis has been conducted on cryptorchidism alone. The purpose of the present study was to use bibliometric analysis to clarify the progress and trend in research on cryptorchidism over the past two decades from the perspective of annual publication outputs, citations, countries, authors, institutions, and keywords with the hope to provide useful references for later research.

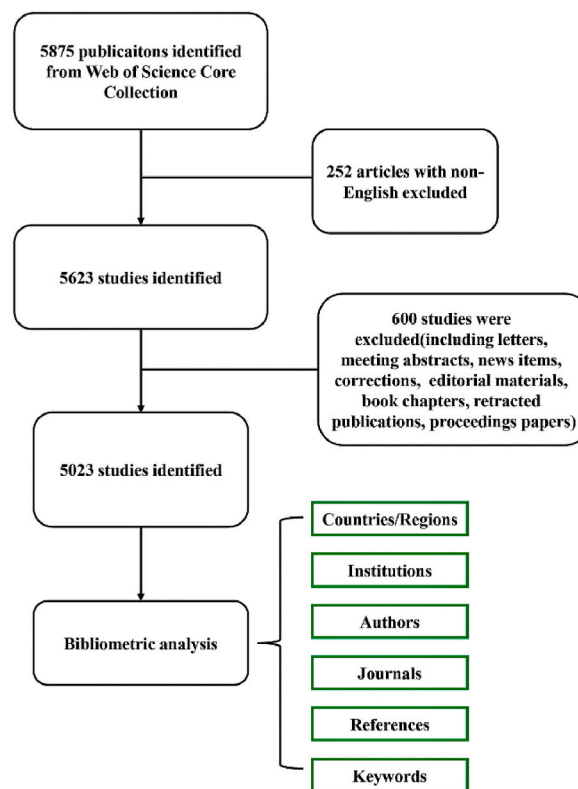


Fig. 1. The flow diagram of literature screening.

2. Materials and methods

2.1. Data collection

The Web of Science (<http://www.webofscience.com>) is the most comprehensive global academic information database, covering natural sciences, social sciences, arts, and humanities [11]. In this study, we selected the Web of Science Core Collection (WoSCC) database as the data source to conduct systematic literature retrieval and data extraction on cryptorchidism from January 1st, 2000 to May 17th, 2022.

To avoid omissions owing to constant database updates, all literature searching and data extraction procedures were completed within the day of May 17th, 2022. The search strategies were described as follows: Topic Search=(cryptorchidism) or (undescended testis) or (ectopic testis). The language was set to English and only original articles or reviews were included for analysis. After extracting the literature dataset, two independent authors applied established inclusion/exclusion criteria to screen publications by reading the titles, abstracts, and whole texts if necessary. A third corresponding author would be consulted before a final decision was made in case of any disagreement. Finally, a total of 5023 documents were saved for the following analyses. The detailed procedures for screening are presented in Fig. 1.

2.2. Bibliometric analysis

The visualizing bibliometric tools, including Tableau Public, Microsoft Excel (2019), VOSviewer (1.6.18.0), and CiteSpace (6.1.R2), were utilized to perform statistical analysis and construct visualization bibliometric networks on cryptorchidism. Knowing that Tableau Public is an open-source software to enable users to visualize the results, we used it to visualize the distribution of publications in analysis of countries/regions and journals [12]. CiteSpace is a program devised for conducting quantitative analysis and constructing network visualization maps, which could be a convenience for scientists and researchers to explore, trace and visualize the emerging research hotspots or radical changes in specific research fields [13]. In the present study, we applied CiteSpace software for performing the co-authorship analysis of institutions, along with co-citation analysis and burstness analysis of references and keywords. We set 1 year as the minimum burst duration. Time slicing was conducted from January 2000 to December 2022, with one year per slice. The top 50 grades of items from each slice were identified for analysis, and other options were set to default. In addition, we further calculated nodes with good centrality (>0.1) in keywords and references, with the aim to identify important pivot points in the field concerned. If the number of network nodes exceeded 350, the function of “compute node centrality” was manually clicked.

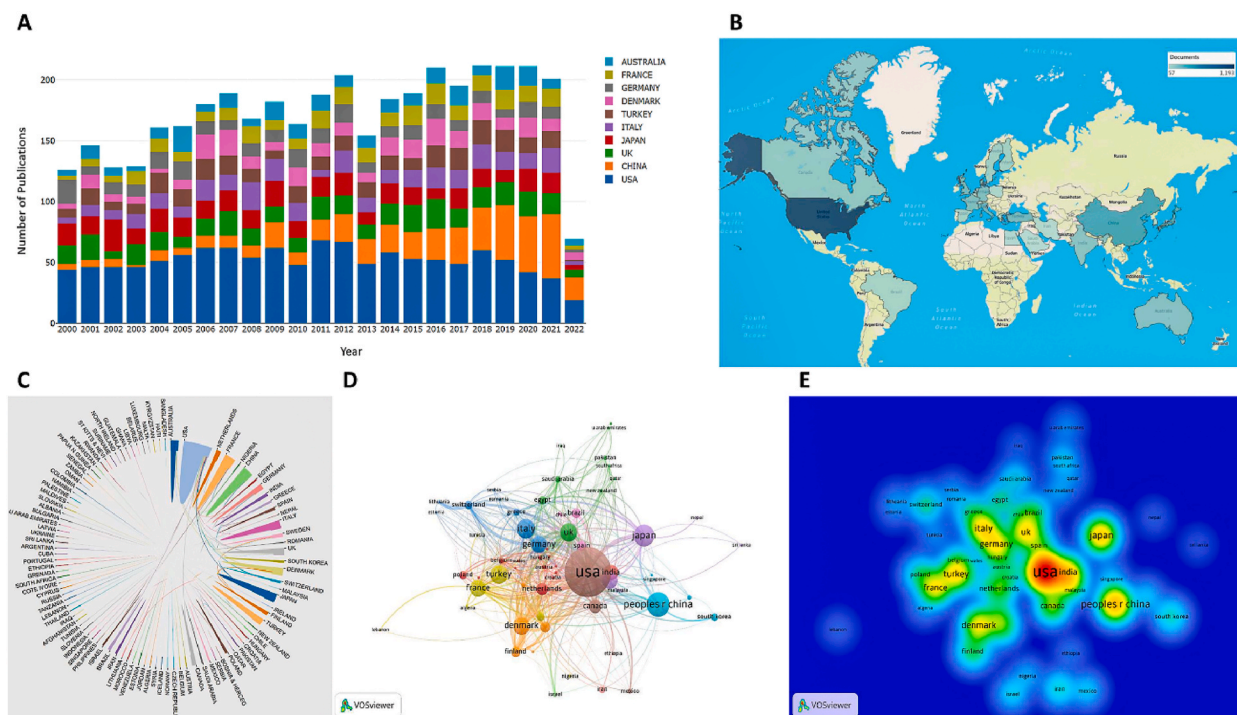


Fig. 2. Publications related to cryptorchidism from 2000 to 2022. (A) The annual number of publications and the growth trend in the top 10 countries/regions. (B) Countries/regions publishing more than 50 papers are presented on the map. (C, D) Visualization maps of the collaboration analysis of countries/regions. The size of nodes represents the article count of a country/region, and the thickness of the lines between two items reflects the strength of collaborations. (E) A density map of literature distribution in countries/regions.

The VOSviewer software is another useful tool for constructing and viewing bibliometric maps, which could be displayed in three or four ways including label views, density views, scatter views, and cluster density views, providing more references for rational decision-making [14]. In our research, VOSviewer provided a platform for the co-authorship analysis (including countries/regions, institutions, and authors), co-citation analysis (including journals and references), and co-occurrence analysis of keywords. The fractional counting method was selected for all elements analyzed by VOSviewer.

3. Results

3.1. Analysis of countries/regions

After rigorous screening by two independent authors (Fig. 1), a total of 5023 papers (including 4485 original research articles and 538 reviews) related to cryptorchidism from 1st January 1st, 2000 to May 17th, 2022 written by 21,754 authors from 114 countries/regions and published in 1170 journals, met our inclusion criteria for bibliometric analysis. As shown in Fig. 2A, the number of annual publications concerning undescended testis in the top 10 countries/regions rose in general and remained at the level of more than 130 papers each year. Of note, Chinese scholars had gradually replaced the United States of America (USA) as the most productive country in this research field since 2020.

Through the Tableau Public application, distributions of the literature concerning cryptorchidism in countries/regions are displayed in Fig. 2B. In addition, the density map intuitively distinguished the most influential countries/regions (Fig. 2E), showing that the primary countries were the USA, China, and Japan. Further, we summarized the number of publications in the top 10 countries/regions (Table 1), which accounted for 77% (3877/5023) of the total outputs. Among these listed countries/regions, the USA (n = 1193) was the most productive country in the field of cryptorchidism, followed by China (n = 427), Japan (n = 358), Italy (n = 309), and Turkey (n = 294). In terms of citations, the papers originating from the USA were cited the most by 40,837 times. In addition, the average citations per publication (ACP) is an indicator of the academic influence, reflecting the comprehensive academic power of countries or authors in some specific areas. Denmark (ACP = 54.04) possessed the highest ACP value, followed by the United Kingdom (ACP = 38.61) and Germany (ACP = 37.65). However, China (ACP = 11.01), as the second most productive country, received a relatively low ACP value.

In this study, we adopted two different methods to conduct the collaboration analysis (Fig. 2C and D). In Fig. 2D, the size of the circles represents the article counts, and the width of lines between two items indicates the strength of collaborations. The USA had close cooperation with Canada, China, Japan, the United Kingdom, and Italy in this field, while the collaboration relationships of other countries/regions were weak.

3.2. Analysis of institutions

The top 10 institutions publishing the largest number of papers and their citations on this topic are listed in Table 2. Among these top 10 institutions, both Denmark and Australia had three institutions that focused on cryptorchidism research, propelling this field forward and deserving more attention. The University of Melbourne in Australia was the leading institution with 131 publications on cryptorchidism, followed by the University of Copenhagen (n = 129), Royal Children's Hospital (n = 97), and the University of Turku (n = 85). In terms of citations, the top 4 institutions were the University of Turku (6163 citations), the University of Copenhagen (5921 citations), the University of Melbourne (4030 citations), and Rigshospitalet Hospital (3950 citations). However, the top 3 institutions with the highest ACP were the University of Turku (72.50 ACP), Rigshospitalet Hospital (54.86 ACP), and the University of Copenhagen (45.89 ACP).

As shown in Fig. 3A, the institutions with a minimal publication count of 15 on cryptorchidism were selected for conducting the collaboration analysis. According to the network visualization, the line between the University of Melbourne and Royal Children's Hospital was the thickest, which manifests a high level of collaboration in this field. And, the University of Melbourne, University of Copenhagen and the Royal Children's Hospital had high-frequency cooperations with external institutions in this field. The inter-agency collaboration relationships were not strong as a whole and need to be strengthened further. In Fig. 3B, the paper published

Table 1

Top 10 countries/regions with the largest number of literature in the field of cryptorchidism.

Rank	Country/region	Publications	Citations	ACP
1	USA	1193	40,837	34.23
2	China	427	4703	11.01
3	Japan	358	7397	12.28
4	Italy	309	9731	31.49
5	Turkey	294	2394	8.14
6	United Kingdom	278	10,735	38.61
7	Denmark	266	14,375	54.04
8	France	253	7601	30.04
9	Germany	252	9490	37.65
10	Australia	247	7423	30.05

ACP, average citations of per publication.

Table 2
Top 10 institutions published the most literature on cryptorchidism.

Rank	Organization and Country	Publications	Citations	ACP
1	University of Melbourne, Australia	131	4030	30.76
2	University of Copenhagen, Denmark	129	5921	45.89
3	Royal Children's Hospital, Australia	97	2122	21.87
4	University of Turku, Finland	85	6163	72.5
5	Murdoch Childrens Research Institute, Australia	73	1186	16.24
6	Rigshospitalet, Denmark	72	3950	54.86
7	Baylor College of Medicine, USA	69	2323	33.68
8	Karolinska Institute, Sweden	68	2949	43.36
9	University of California, San Francisco, USA	46	1734	37.69
10	Aarhus University Hospital, Denmark	42	1121	26.69

ACP, average citations of per publication.

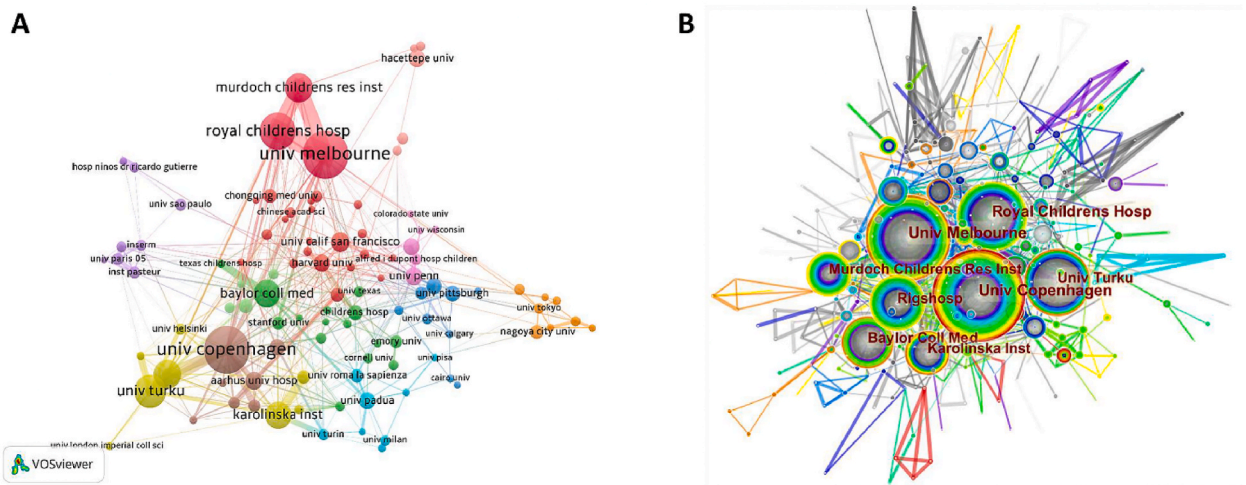


Fig. 3. Contributions of different organizations to publications. (A) VOSviewer visualization map of the collaboration analysis of institutions. **(B)** CiteSpace visualization map of the collaboration analysis of institutions. The occurrences of one institution are measured by the size of the circle.

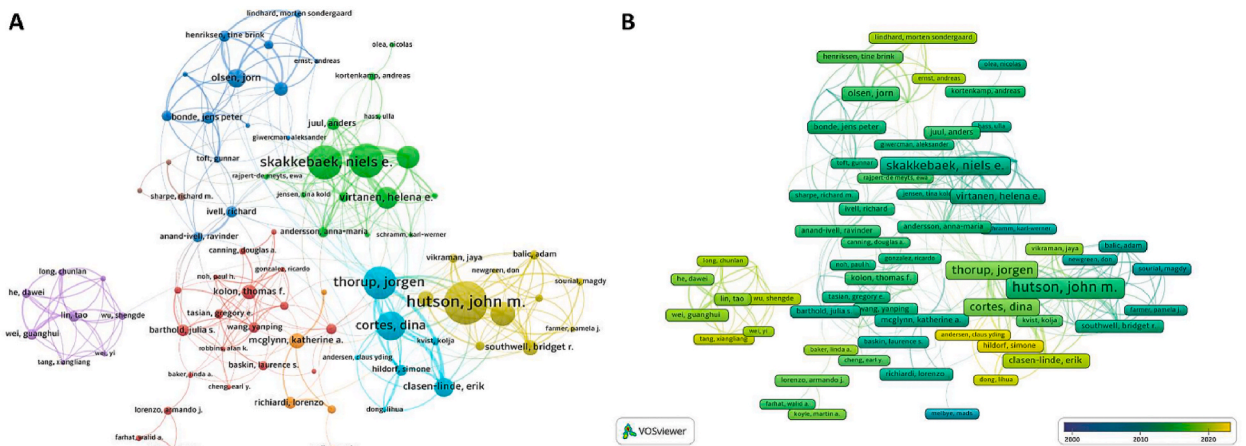


Fig. 4. Visualization map of research authors. (A) VOSviewer visualization map of the collaboration analysis of authors who published more than 6 papers. **(B)** Overlay visualization map of the co-authorship network (the closer to yellow means, the nearer the time of publication).

date of one institution is depicted by gradient color, from gray (early) to red (recent). As far as cryptorchidism is concerned, the University of Copenhagen has obtained many achievements concerning cryptorchidism research in recent years.

3.3. Analysis of authors

The VOSviewer software was applied to further obtain an objective evaluation of researchers who specialized in cryptorchidism. In this study, a total of 251 authors with 6 or more publications were screened for co-authorship analysis, who were considered as the core author groups based on Price's Law [15], and then the set of those with collaborative associations was selected to map the collaborative network, containing 82 authors. In Fig. 4A, the area of nodes represents the author's publication count, and the thickness of lines between two authors indicates the strength of collaborations. We could clearly figure out that these authors were categorized into several clusters represented by distinct colors to show the core author groups in cryptorchidism research. Authors like "Hutson, John M.", "Thorup, Jorgen" and "Skakkebaek, Niels E." played essential roles in their clusters, implying that these authors took the lead in this research field. However, each cluster had less cooperation with the others. Fig. 4B shows the publication trends of researchers by gradient colors (towards yellow indicating more recent publication time). Some authors such as "Clasen-Linde, Erik", "Hildorf, Simone Engmann" and "Andersen, Claus Yding" have published some new articles in recent years. Meanwhile, Chinese authors have published large numbers of articles in the past five years. China's research in this field has gradually become more prominent.

The top 10 most productive authors are shown in Table 3. "Hutson, John M." from Royal Children's Hospital Melbourne, published the largest number of papers ($n = 51$), followed by "Skakkebaek, Niels E." and "Thorup, Jorgen" ($n = 40$). What deserves particular attention is that four authors on the top 10 most productive list are from the University of Copenhagen. As for citations, "Skakkebaek, Niels E." enjoyed the most citations ($n = 4441$) with a significantly higher H-Index [16] as compared with other researchers, and therefore his work has attracted widespread attention in the field concerned.

3.4. Analysis of journals

In VOSviewer software, we set the minimum cited frequency of a journal to 50 times, and 418 out of 11,359 journals were selected to construct a co-cited network of journals. As shown in Fig. 5A and clusters are represented by different colors, and the size of nodes indicates the citation frequency of a journal. Apparently, the *JOURNAL OF UROLOGY* and *JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM* were the symbols of the top two largest clusters. The cross-citation analysis of journals is presented in Fig. 5B, showing that the *JOURNAL OF UROLOGY* had close relationships with *JOURNAL OF PEDIATRIC UROLOGY*, *JOURNAL OF PEDIATRIC SURGERY*, *PEDIATRIC SURGERY INTERNATIONAL*, and that these journals had greater interest in this topic.

The top 10 journals that published the largest number of cryptorchidism-related papers are listed in Fig. 5C and Table 4, showing that the *JOURNAL OF UROLOGY* (IF = 7.6) as the leading journal publishing the largest number of papers ($n = 225$), cited 6790 times. There were 180 publications in *JOURNAL OF PEDIATRIC SURGERY* (IF = 2.549), 140 publications in *JOURNAL OF PEDIATRIC UROLOGY* (IF = 1.921), and 117 publications in *AMERICAN JOURNAL OF MEDICAL GENETICS PART A* (IF = 2.578). The *JOURNAL OF UROLOGY* enjoyed the highest citations (6790), but the number of ACP was 30.17. However, *HUMAN REPRODUCTION* (62.38 ACP) and *JOURNAL CLINICAL ENDOCRINOLOGY & METABOLISM* (59.70 ACP) had relatively high ACP, indicating that studies regarding cryptorchidism in both journals had powerful academic influence.

3.5. Analysis of references

Co-citation analysis of references was performed using the VOSviewer program, and the minimally cited number of a reference was set as 50. Of the 87,705 references cited by these extracted papers, 145 references were included for analysis. As depicted in Fig. 6A, these references were clustered into three groups which are represented by distinct colors. Tables 5 and 6 show the top 10 most cited references about the frequency and centrality, which were primarily involved in the prevalence, pathological mechanism, and treatment of cryptorchidism. For example, Stephan et al. identified that a target deletion of the *Ins13* gene could lead to bilateral cryptorchidism [17]. As for frequency, the most frequently co-cited reference receiving 330 citations was *Testicular dysgenesis*

Table 3
Top 10 authors ranked by publication counts on cryptorchidism.

Rank	Author	Country	Affiliation	Publications	Citations	ACP	H-Index
1	Hutson, John M.	Australia	Royal Children's Hospital Melbourne	51	884	17.33	46
2	Skakkebaek, Niels E.	Denmark	University of Copenhagen	40	4441	111.02	116
3	Toppari, Jorma	Finland	University of Turku	40	2642	66.05	77
4	Thorup, Jorgen	Denmark	University of Copenhagen	39	720	25.71	28
5	Cortes, Dina	Denmark	University of Copenhagen	34	656	19.29	29
6	Li, Ruili	China	Air Force Military Medical University	28	396	14.14	28
7	Main, Katharina M.	Denmark	University of Copenhagen	27	1874	67.67	65
8	Hadziselimovic, Faruk	Switzerland	Childrens Day Care Center Liestal	26	423	16.27	34
9	Virtanen, Helena E.	Finland	University of Turku	26	1396	53.69	32
10	Hayashi, Yutaro	Japan	Nagoya City University	25	297	11.88	20

ACP, average citations of per publication.

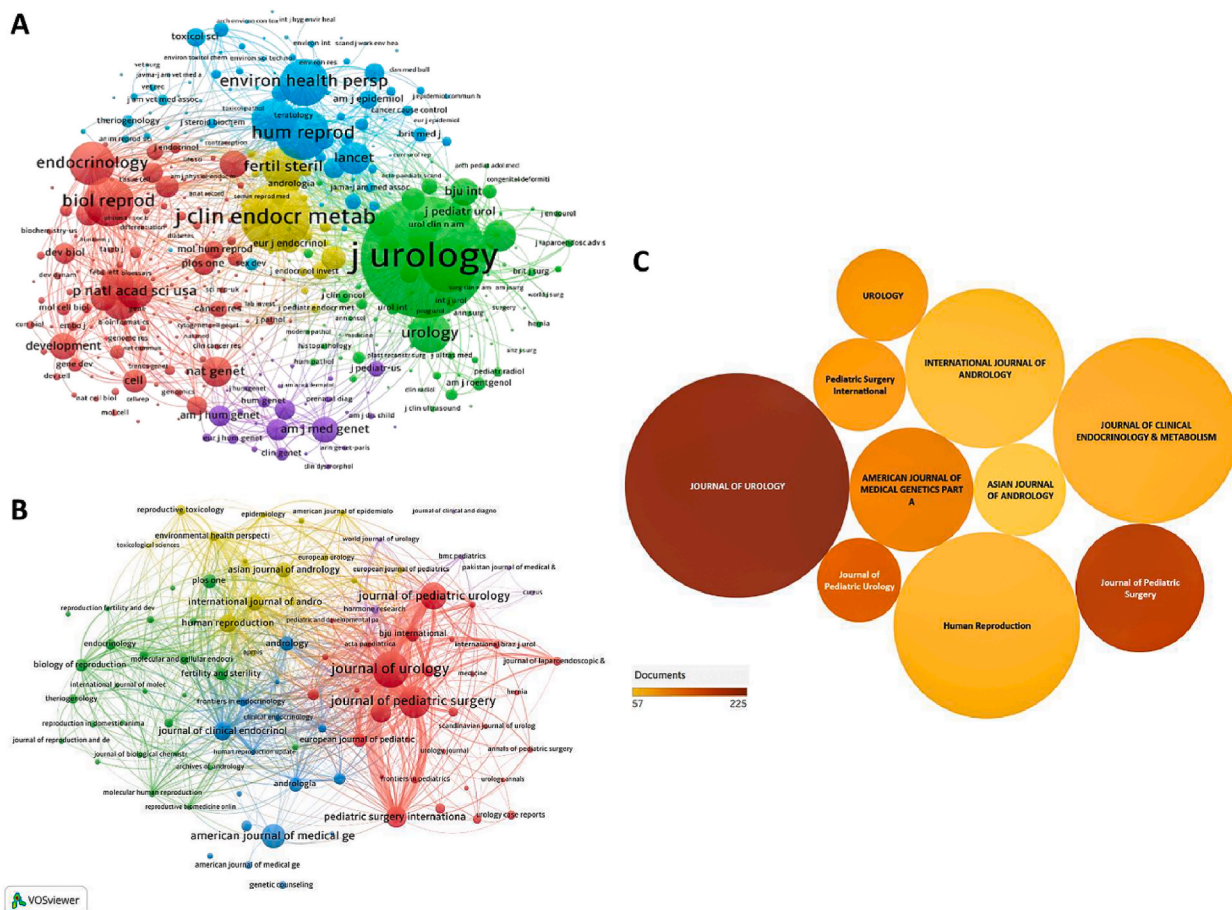


Fig. 5. Visualization map of journals. (A) VOSviewer visualization map of co-cited journals. (B) Cross-citation analysis of journals. The thickness of the lines between two items indicates the strength with that they cited each other. (C) The top 10 journals that produced the largest number of papers were based on Tableau Public software. The size of the circle represents the number of citations, and the color represents the number of publications.

Table 4
Top 10 journals with the largest number of publications in the field of cryptorchidism.

Rank	Journals	Publications	IF/Q	Citations	ACP
1	JOURNAL OF UROLOGY	225	7.6/Q1	6790	30.17
2	JOURNAL OF PEDIATRIC SURGERY	180	2.549/Q2	2227	12.37
3	JOURNAL OF PEDIATRIC UROLOGY	140	1.921/Q3	958	6.84
4	AMERICAN JOURNAL OF MEDICAL GENETICS PART A	117	2.578/Q3	2075	17.73
5	PEDIATRIC SURGERY INTERNATIONAL	95	2.003/Q3	1164	12.25
6	UROLOGY	94	2.633/Q3	1138	12.1
7	JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM	78	6.134/Q1	4657	59.7
8	HUMAN REPRODUCTION	75	6.353/Q1	4679	62.38
9	INTERNATIONAL JOURNAL OF ANDROLOGY	67	NA	3437	51.29
10	ASIAN JOURNAL OF ANDROLOGY	57	3.054/Q2	1159	20.33

IF, impact factor (2021); ACP, average citations of per publication; Q, quartile in category (2021); NA, not applicable.

syndrome: an increasingly common developmental disorder with environmental aspects, which was published in *HUMAN REPRODUCTION*, reporting that testicular dysgenesis syndrome including undescended testis was increasingly common as a result of adverse environmental factors [18]. In terms of centrality, the article ranking first (centrality = 0.19) was *Epidemiology and pathogenesis of cryptorchidism* published on *HUMAN REPRODUCTION UPDATE*, which further summarized the epidemiology and risk factors of cryptorchidism [19]. In addition, the references were clustered into 10 patterns using the CiteSpace software (Fig. 6B), of which the top 5 clusters were “testicular cancer” (Cluster 0, n = 103), “insulin-like factor” (Cluster 1, n = 92), “retrospective multicenter analysis” (Cluster 2, n = 90), “young children” (Cluster 3, n = 85), and “maternal residential exposure” (Cluster 4, n = 83). The most relevant

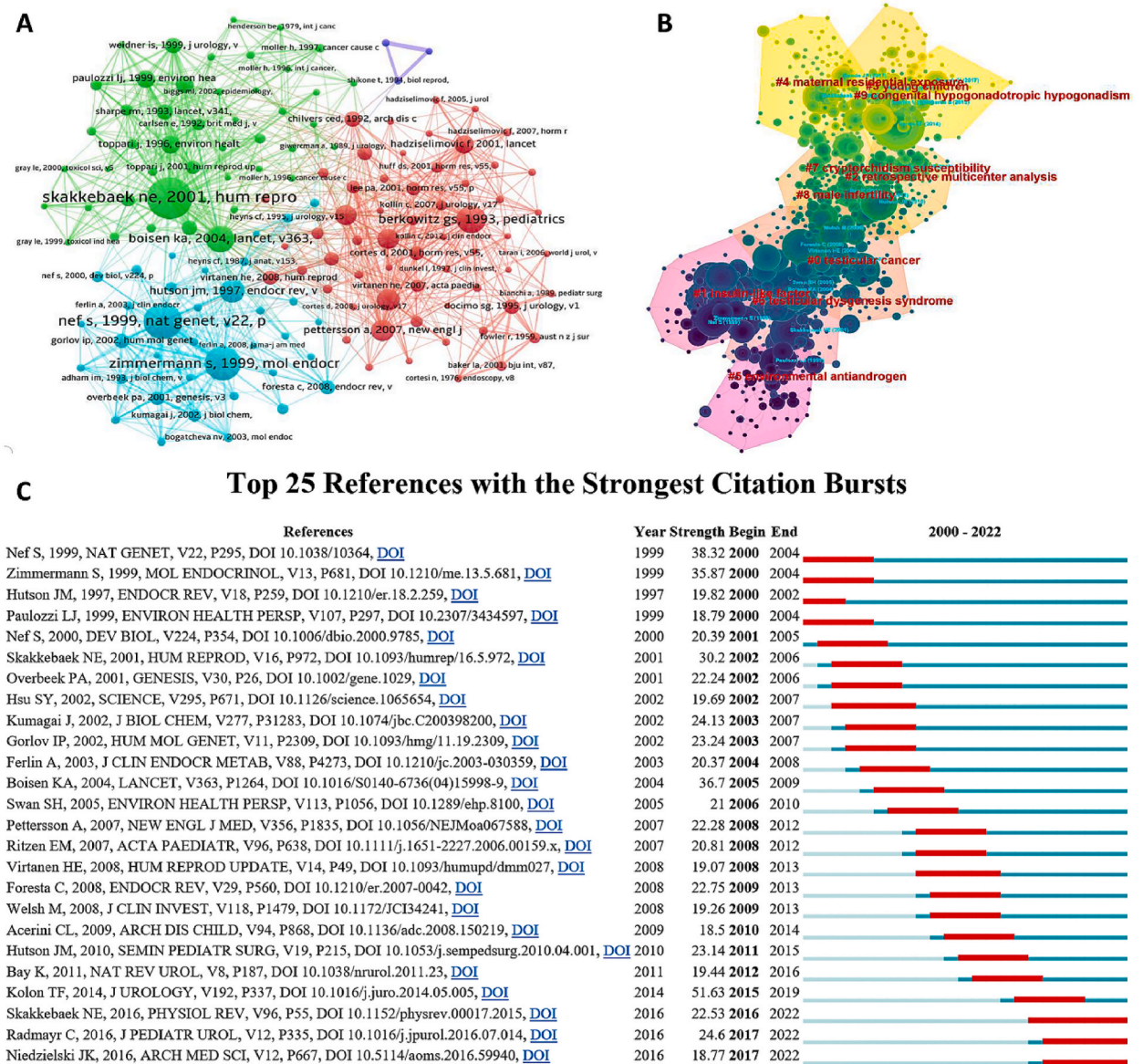


Fig. 6. Visualization map of co-cited references. (A) Co-citation network of references by VOSviewer. (B) Cluster analysis of references. (C) Top 25 references with the strongest citation bursts.

citer to the largest cluster 0 was the *Role of hormones, genes, and environment in human cryptorchidism* [20], which was published on *ENDOCRINE REVIEWS*.

Bursts analysis can provide insights into the development of research hotspots, trends, and frontier dynamics within a certain period. The top 25 references with the strongest citation bursts are screened in Fig. 6C. Among them, Kolon TF, 2014, *J UROLOGY*, V192, P337 [21] had the highest burst strength (n = 51.63), entitled *Evaluation and treatment of cryptorchidism: AUA guideline*, which kept citation popularity between 2015 and 2019. Meanwhile, from 2016 to 2022, three references with good citation bursts are *Male Reproductive Disorders and Fertility Trends: Influences of Environment and Genetic Susceptibility* [22], *Management of undescended testes: European Association of Urology/European Society for Paediatric Urology Guidelines* [23], and *Undescended testis - current trends and guidelines: a review of the literature* [24]. It is clear from reading the above literature that the research hotspots in recent years mainly focus on exploring the optimal treatment mode for cryptorchidism.

Table 5
Top 10 cited references by the total citations.

Rank	Title	Corresponding authors	Journal	Publication year	Impact factor(2021)	Citations
1	Testicular dysgenesis syndrome: an increasingly common developmental disorder with environmental aspects	N.E.Skakkebaek	HUMAN REPRODUCTION	2001	6.353	330
2	Cryptorchidism in mice mutant for Insl3	Luis F. Parada	NATURE GENETICS	1999	41.307	280
3	Targeted disruption of the Insl3 gene causes bilateral cryptorchidism	Stephan Zimmermann	MOLECULAR ENDOCRINOLOGY	1999	NA	267
4	Prevalence and natural history of cryptorchidism	Gertrud S. Berkowitz	PEDIATRICS	1993	9.703	213
5	Difference in prevalence of congenital Cryptorchidism in infants between two Nordic countries	Jorma Toppari	LANCET	2004	202.731	212
6	Anatomical and functional aspects of testicular descent and cryptorchidism	John M. Hutson	ENDOCRINE REVIEWS	1997	25.261	184
7	Evaluation and treatment of cryptorchidism: AUA guideline	Thomas F. Kolon	JOURNAL OF UROLOGY	2014	7.6	167
8	Age at surgery for undescended testis and risk of testicular cancer	Andreas Pettersson	NEW ENGLAND JOURNAL OF MEDICINE	2007	176.079	167
9	The epidemiology of congenital cryptorchidism, testicular ascent and orchiopexy	Julia Spencer Barthold	JOURNAL OF UROLOGY	2003	7.6	158
10	Nordic consensus on treatment of undescended testes	E. Martin Ritz'en	ACTA PAEDIATRICA	2007	4.056	157

NA, not applicable.

Table 6
Top 10 cited references by the centrality.

Rank	Title	Corresponding authors	Journal	Publication year	Impact factor (2021)	Centrality
1	Epidemiology and pathogenesis of cryptorchidism	J Toppari	HUMAN REPRODUCTION UPDATE	2008	17.179	0.19
2	T222P mutation of the insulin-like 3 hormone receptor LGR8 is associated with testicular maldescent and hinders receptor expression on the cell surface membrane	Alexander I Agoulnik	AMERICAN JOURNAL OF PHYSIOLOGY- ENDOCRINOLOGY AND METABOLISM	2007	5.9	0.14
3	Risk factors for congenital cryptorchidism in a prospective birth cohort study	Ida N Damgaard	PLOS ONE	2008	3.752	0.14
4	Fertility potential in a cohort of 65 men with previously acquired undescended testes	Jocelyn van Brakel	JOURNAL OF PEDIATRIC SURGERY	2014	2.549	0.14
5	The 'oestrogen hypothesis' - where do we stand now?	Richard M Sharpe	INTERNATIONAL JOURNAL OF ANDROLOGY	2003	NA	0.14
6	The epidemiologic evidence linking prenatal and postnatal exposure to endocrine disrupting chemicals with male reproductive disorders: a systematic review and meta-analysis	Jens Peter Bonde	HUMAN REPRODUCTION UPDATE	2017	17.179	0.13
7	Foetal exposure to phthalate esters and anogenital distance in male newborns	Yayoi Suzuki	INTERNATIONAL JOURNAL OF ANDROLOGY	2012	NA	0.13
8	Journal of Pediatric Surgery-Sponsored Fred McLoed Lecture. Undescended testis: the underlying mechanisms and the effects on germ cells that cause infertility and cancer	John M Hutson	JOURNAL OF PEDIATRIC SURGERY	2013	2.549	0.1
9	Age at orchiopexy and testis palpability predict germ and Leydig cell loss: clinical predictors of adverse histological features of cryptorchidism	Laurence S Baskin	JOURNAL OF UROLOGY	2009	7.6	0.1
10	Cord blood insulin-like peptide 3 (INSL3) but not testosterone is reduced in idiopathic cryptorchidism	Patrick Fénelichel	CLINICAL ENDOCRINOLOGY	2015	3.523	0.1

NA, not applicable.

3.6. Analysis of keywords

3.6.1. Co-occurrence network

Using VOSviewer software, we extracted 9776 keywords from 5023 publications, and 551 keywords that appeared more than 5 times are shown in Fig. 7A. The top 10 keywords about the frequency and centrality of cryptorchidism are shown in Table 7.

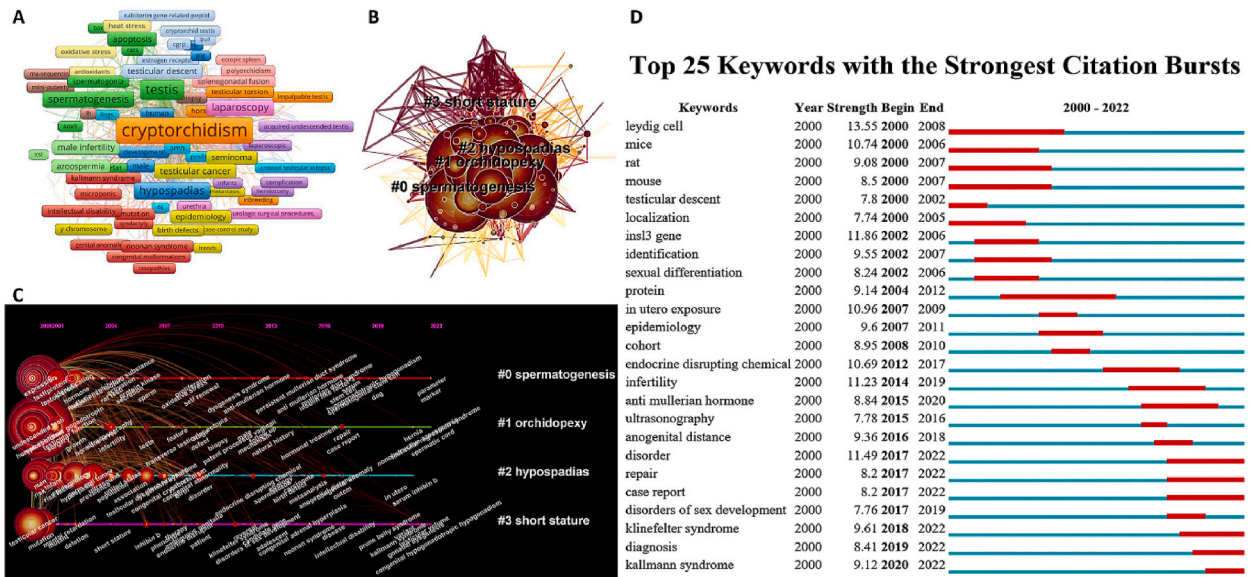


Fig. 7. Keyword mapping of studies on cryptorchidism. (A) VOSviewer visualization map of co-occurrence keywords. (B) Clustering analysis of co-occurrence keywords based on CiteSpace software. (C) A timeline view of keywords from 2000 to 2022. (D) Top 25 keywords with the strongest citation bursts. The red line indicates a period when the corresponding keywords frequently appeared.

Table 7

Top 10 keywords by the occurrences and centrality.

Rank	Occurrences	Keyword	Rank	Centrality	Keyword
1	1386	Cryptorchidism	1	0.14	Testicular cancer
2	489	Testis	2	0.14	Testosterone
3	261	Hypospadias	3	0.12	Sertoli cell
4	261	Undescended testis	4	0.11	Testis
5	164	Laparoscopy	5	0.1	Pregnancy
6	164	Spermatogenesis	6	0.09	Men
7	156	Orchiopexy	7	0.09	Diagnosis
8	152	Orchidopexy	8	0.09	Semen quality
9	140	Infertility	9	0.08	Mutation
10	110	Testicular cancer	10	0.08	Follicle stimulating hormone

“Cryptorchidism” was the most frequently used keyword in this topic (1386 times) over the past two decades, followed by “testis” (489 times), “hypospadias” (261 times), and “undescended testis” (261 times). With respect to centrality, the popular keywords were “testicular cancer,” “testosterone,” “Sertoli cell,” “testis,” and “pregnancy”. Clustering analysis of keywords using CiteSpace software revealed a total of 4 clusters, including “spermatogenesis,” “orchidopexy,” “hypospadias” and “short stature” (Fig. 7B). In addition, we used the software CiteSpace to establish a timeline map of keyword clusters to further determine the research trends (Fig. 7C). The prevalence, pathogenesis, risk factors, and sequels (such as testicular cancer and infertility) began receiving more attention in the early stage. From the mid-to-late period, researchers have shown great interest in treatments (such as orchidopexy and hormonal therapy) and some congenital genetic disorders that are accompanied by cryptorchidism.

3.6.2. Burst keyword analysis

Burst keyword analysis was performed simultaneously to reflect research hotspots and frontiers on cryptorchidism. The top 25 keywords with the strongest citation bursts from 2000 to 2022 are listed in Fig. 7D. The keywords with the good burst value were “Leydig cell (n = 13.55),” “insl3 gene (n = 11.86),” “disorder (n = 11.49),” and “infertility (n = 11.23)”. Additionally, “disorder,” “Klinefelter syndrome,” “Kallmann syndrome,” “diagnosis,” and “disorders of sex development” were the emerging outburst keywords in recent years, which can be regarded as the current research hotspots in this field.

4. Discussion

Cryptorchidism refers to unilateral or bilateral undescended testes due to anatomical and hormonal factors [7]. Cryptorchidism is the most common congenital abnormality in the genital system at birth, which may lead to testicular dysfunction or infertility in severe cases. Currently, the etiology, adverse effects, and treatments of undescended testis have attracted increasing attention [25–27]. With

the research progressing, more efforts have been focused on identifying or tracing the research status and hotspots of cryptorchidism.

In this bibliometric analysis, we presented an overview of cryptorchidism from various perspectives using visualization maps and tables. The number of annual publications increased gradually from January 1st, 2000 to May 17th, 2022, indicating increasing attention on cryptorchidism during this period. The USA remained the most productive country in promoting the research on cryptorchidism, with 1193 publications and 40,837 citations, enjoying a leading position in this field. However, China has exceeded the USA in the number of annual papers in recent years, and the possible causes are the advance in scientific prowess and the increase in the number of scientific research groups. It is noteworthy that Denmark ranked 7th with 266 papers, but received 54.04 ACP, showing remarkable contributions in this field. Conversely, publications from China had relatively fewer citations, suggesting that its academic influence in this field is limited and therefore Chinese researchers should further improve the scope and depth of research in future. With respect to institutions, we identified that 6 of the top 10 institutions that generated the largest number of papers were from Denmark and Australia, and it is equally important that many core authors were from these institutions. Therefore, it is prudent to suggest that the scientific community in this field should strengthen international cooperation with these institutions.

Analysis showed that “Hutson, John M”, “Skakkebaek, Niels E”, and “Toppari, Jorma” were the primary authors who produced a high volume of documents. Among these documents, a review written by John M Hutson, published in the journal of *ENDOCRINE REVIEWS*, summarizes the normal process of testicular descent under both the anatomical remodeling and hormonal control, and further discussed the etiology of cryptorchidism (including inherited syndromes) and corresponding management [28]. Due to the complexity of the testicular descent process, the mechanism of cryptorchidism remains elusive. In addition, Hutson et al. also published a highly informative paper concerning the anatomical and functional testicular descent in 1997 [29]. Skakkebaek et al. put forward the concept of testicular dysgenesis syndrome (TDS) composed of cryptorchidism and other three symptoms, suggesting that adverse environmental factors were probably potential causes for TDS, leaving significant influence for following research [18]. Correspondingly, Toppari et al. further investigated the relationship between environmental risk factors and cryptorchidism. A prospective study reported that the concentration of polybrominated diphenyl ethers (PBDE) in breast milk was associated with congenital undescended testis, as a result of fetal exposure to PBDE [30]. In addition, maternal consumption of food containing polychlorinated biphenyls, maternal smoking, premature birth, low birth weight, and gestational diabetes were associated with the risk of cryptorchidism [2,31–33].

Among the top 10 journals with the most documents concerning cryptorchidism, three journals were in Q1 (Q represents quartile in category, 2021), with the corresponding impact factor (IF) exceeding 5. The *JOURNAL OF UROLOGY* published the largest number of papers ($n = 225$) in this field during the past two decades, with 6790 citations and 30.17 ACP, obtaining wide recognition from the scientific community. Nonetheless, *HUMAN REPRODUCTION* gained the highest ACP ($n = 62.38$), manifesting a comparable higher academic influence. Cross-citation analysis showed that *JOURNAL OF PEDIATRIC SURGERY* and *JOURNAL OF PEDIATRIC UROLOGY* had the strongest cross-citation relationship. Thus, relevant researchers could trace the latest research progress and tendency of undescended testis by noticing the above-mentioned journals for more literature support.

The higher centrality of a node represents greater influence and importance in the field. According to the analysis of references and keywords in centrality, combined with the corresponding cluster patterns, exploring the risk factors, pathogenesis (especially for gene *INSL3*), and sequels (mainly testicular cancer and infertility) of cryptorchidism has received extensive attention. At present, a variety of factors such as hormones, maternal factors, endocrine-disrupting chemicals, alcohol, and drugs have become important incentives for cryptorchidism research [34]. In recent years, maternal exposure has been a subject of profound interest to researchers [35,36], showing consistency with Cluster 4 in the reference clustering analysis. However, a considerable number of etiological studies are putative, of which there is little consistent evidence to support an association with cryptorchidism. More well-designed quality studies are required in future. From the perspective of pathogenesis, the gene *INSL3* has become the focus of the most attention in this field, particularly between 2002 and 2006 (see burst analysis, $n = 11.86$). Insulin-like factor 3 (*INSL3*) encodes a member of the insulin-like hormone superfamily. The encoded protein is mainly produced in Leydig cells of the testes. As early as 1999, Zimmermann et al. observed that targeted impairment of the *INSL3* gene in male mice led to bilateral cryptorchidism, implying its important role in the testicular descent process [17]. Faruk et al. found that the smooth muscle tissue of epididymis was abnormally developed in *INSL3* homozygous mutant mice [37]. Given the incidence of the *INSL3* genetic mutations less than 10% in males who experienced cryptorchidism, other risk factors may exist [28]. Some researchers further demonstrated that targeted disruption of the relaxin family peptide receptor 2 (*RXFP2*, the receptor of *INSL3*) or its mutation was also associated with undescended testis [4,38–40]. It was the integrity of the *INSL3/RXFP2* signaling pathway that had a significant effect on testicular descent in the transabdominal stage. Furthermore, the expression of androgen receptors in the gubernaculum was regulated by *INSL3*, which played an important role in the inguinoscrotal stage of testicular descent through the canonical Wnt signaling pathway [41–43]. In addition, several pathogenic genes, including those associated with congenital hypogonadotropic hypogonadism such as *GNRH1/GNRHR*, *KISS1/KISSR*, and *TAC3/TACR3*, as well as genes involved in androgen synthesis and action like *LHCGR* and *AR*, and estrogen receptor genes, are closely associated with cryptorchidism [43–45]. The exploration of pathogenic/susceptible genes related to cryptorchidism has been continuously advancing in recent years, although the specific mechanisms underlying the disease remain unclear and warrant further investigation. Integrative genetic research holds promise for precise diagnosis and treatment of cryptorchidism, and in guiding clinical decision-making.

Testicular cancer and infertility have been recognized as the two most serious sequels of cryptorchidism. At present, the mechanism of the malignant transformation of cryptorchidism into testicular cancer is generally thought to relate to such factors as elevated testicular temperature, abnormal spermatogenic cells, and gonadal dysplasia. Loebenstein et al. suggested that malignancy in males with previous cryptorchidism may result from abnormal germ cell development during minipuberty [44]. The suspected cause may be the gradual transformation of immature gonocytes into precancerous cells, forming intraductal germ cell tumors, which then develop

into testicular cancer after puberty [45]. Some studies suggest that the age at which children undergo orchidopexy may affect the risk of subsequent testicular malignancy [46,47]. Regardless of the age at which surgery is performed, the risk of testicular malignancy is still higher than those without a history of cryptorchidism. The cause of malignant transformation of cryptorchidism remains largely unclear.

As for infertility, increased testicular temperature is also undoubtedly an important cause, which results in the impaired transformation of juvenile germ cells to adult dark spermatogonia. In addition, genetic factors are also important causes of infertility in patients with cryptorchidism, especially in patients who are still diagnosed with high-risk infertility despite timely orchiopey [48]. Ferlin et al. reported that mutation in the gene steroidogenic factor 1 (NR5A1) was a novel genetic cause of infertility in patients with cryptorchidism [49]. Mehta et al. identified that mutations in the desert hedgehog (DHH) gene impacted reproduction, leading to infertility and gonadal dysgenesis in cryptorchidism patients [50]. Presently, there remains a contentious debate regarding the optimal strategies for preserving the fertility potential of individuals with cryptorchidism, particularly with respect to the utilization of hormonal therapy. Adequate treatment with low-dose GnRHa has been shown to enable 86% males to achieve a normal sperm count and prevent the occurrence of azoospermia [51]. Some recent studies have shown that the fertility outcome can be enhanced by the administration of low-dose every-second-day postoperative LHRH treatment in bilateral cryptorchidism [52]. However, there is no consensus regarding the use of hormonal therapy for preventing infertility in patients with cryptorchidism. More efforts are required to effectively improve the treatment of salvaging infertility in cryptorchidic patients.

Subsequently, burst analysis of references and keywords was conducted to further explore the trajectory of research trends or hotspots. Reference analysis showed that exploration of the optimal treatment for cryptorchidism remains a research hotspot in recent years, especially in prevention of infertility. Early orchiopey is now the treatment of choice for cryptorchidism, while no consensus exists on hormonal therapy. The quality of most research on hormonal therapy is unsatisfactory, and many discrepancies exist in testicular location, patient populations, and timing and dosage of hormone administration. In addition, there is a significant lack of long-term follow-up data. Given that some patients continue to suffer germ cell apoptosis and consequent decline in sperm production after hormone therapy, which in turn leads to infertility [53], it is particularly important to identify patients who can benefit from hormone therapy. However, there is a lack of relevant clinical data. Existing evidence has shown that environmental exposure is the most important factor causing male reproductive infertility in TDS patients, and these environmental factors can affect several generations via epigenetic mechanisms [22]. Husmann et al. called for the use of microscopic techniques to guide treatment from the genetic perspective instead of blindly pursuing multiple hormonal treatments that may lead to infertility (45). Whether their suggestion is safe and practical needs to be confirmed by more studies and clinical trials.

Burst analysis of keywords, combined with the cluster analysis of references (cluster 9) of the present study shows that increasing attention has been paid to congenital hypogonadotropic hypogonadism, especially Kallmann syndrome and Klinefelter syndrome, knowing that both syndromes share some clinical signs including cryptorchidism [54–56]. Both syndromes result in disorders of sex development (DSD). An overview of the literature in recent years shows that research on congenital hypogonadotropic hypogonadism is mostly focused on genetic mechanisms, particularly genetic mutations. In addition, there is a lack of long-term results to assess the effect of hormone therapy for this type of disease on adult fertility, and more high-quality studies are required in this respect [57].

4.1. Strengths and limitations

To the best of our knowledge, this is the first study to summarize the status of cryptorchidism research over the past two decades by using bibliometrics analysis. Through a systematic analysis of the features of countries, institutions, authors, keywords, references, and other factors, this paper provides a complete profile of the current research status and future trends in this field. Nonetheless, some limitations are unavoidable. For instance, we only collected documents from the WoSCC database and only included reviews and original articles written in English, which may to some extent affect the accuracy of the results. In addition, the constant updating of the database can also lead to slight deviations in the results.

5. Conclusion

Cryptorchidism has attracted increasing attention from the scientific community concerned. The USA remains the leader in this field, and Chinese contributions are increasing rapidly. There has been a notable upsurge in international collaboration within the field, and it is imperative to continue advancing collaborative endeavors between domestic and foreign scholars. Finally, exploration of the optimal treatment modality for cryptorchidism, especially in the prevention of adult infertility, remains a major future focus. High-quality follow-up studies are needed in future. Furthermore, the pathogenesis (especially at the genetic level) and treatment of hypogonadism (such as Kallmann syndrome and Klinefelter syndrome) have attracted more attention of more researchers in recent years.

Author contribution statement

Xiaodu Xie; Jian Hu: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Lumiao Liu; Pan Lei; Peng Zhang; Chongjun Ran: Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

Peihe Liang: Conceived and designed the experiments.

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Data availability statement

Data will be made available on request.

Additional information

No additional information is available for this paper.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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