

Research Article

Bibliometric Analysis of Hypospadias Research

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Abstract

Hypospadias involves abnormal urethral meatus positioning, with varying severity and potential syndromic associations. While surgery is the standard treatment, outcomes often disappoint, impacting physical and mental health. Recent research has heightened attention on its causes and surgical management, leading to a surge in related publications. This study used bibliometric analysis tools (bibliometrix R package, VOSviewer, and CiteSpace) to examine 3,647 publications by 14,633 authors, identifying seven clusters focused on diagnosis, pathophysiology, and treatment. Key research areas include genetic mechanisms, environmental factors, surgical outcomes, anesthesia techniques, and post-surgery patient satisfaction. Emerging areas include the precise selection of surgical flap sources, genomic alterations, and associations with sex development disorders, suggesting promising avenues for future research. This bibliometric analysis offers a comprehensive view of current research trends and hotspots in hypospadias, contributing to a deeper understanding of the field and informing future research directions.

Keywords: Hypospadias; Bibliometric analysis; Genetic mechanisms; Surgical outcomes; Environmental factors

Introduction

Hypospadias is a common birth defect in boys that affects the genitals and is characterized by an abnormal positioning of the urethral opening due to atypical development of the urethral corpus cavernosum. Hypospadias often coexists with other genital abnormalities such as penile curvature and irregular penile skin. In addition to its anatomical implications, hypospadias significantly impacts the patient's physiological and mental well-being. Epidemiological studies indicate that hypospadias is one of the most prevalent congenital structural penile malformations, ranking second only to cryptorchidism in male genital birth defects. The incidence of hypospadias is increasing, currently affecting approximately 1 in 200–250 individuals, and as a result it has attracted considerable attention within the medical community. Despite ongoing research, the exact cause of hypospadias remains unknown due to its complex pathogenesis and diverse clinical presentations. Some cases are associated with specific syndromes, which complicates both the study and treatment of the condition. Surgical intervention is the primary treatment for hypospadias, with approximately 300 surgical techniques available. However, regardless of the chosen method, postoperative complications are common, posing risks to the physical and mental health of affected children. As such, addressing how to minimize complications and improve surgical success rates is a critical issue in the medical field. Recent years have witnessed a surge in domestic and international research on hypospadias, leading to the expansion of academic literature and information overload. This abundance of data not only complicates the identification of current

research trends in the field but also hampers new research initiatives, limiting the scope and depth of exploration. Given this intricate research landscape, streamlining the integration of information and identifying useful directions for research are essential for advancing hypospadias studies.

Bibliometrics, a method that involves the statistical analysis of published research to extract measurable data, illustrates how knowledge is utilized in publications, offers a comprehensive understanding of the research field, and sheds light on the evolution and changes within the research area. Bibliometrics also assists in identifying influential studies or scholars, providing researchers with a clearer perspective on research topics and uncovering the strengths and weaknesses of research. As a result, bibliometric analysis has gained popularity across various fields in recent years.

Fardod O'Kelly et al. have conducted bibliometric analyses of the top 150 highly cited publications on hypospadias. Doğan G et al. have also performed bibliometric analyses on the publications of hypospadias. Together, these studies have provided valuable insights into future research trends and have created new knowledge framework maps for researchers. However, there remains a lack of comprehensive systematic analysis of the literature on hypospadias. With the increasing number of publications on this topic, it is crucial to systematically review the scientific knowledge structure within the literature, understand research trends, and identify hotspots in the field. Building on previous research, we conducted a bibliometric

analysis of the literature on hypospadias from 1998 to 2023, with the aim of comprehensively assessing research trends and hotspots using the Web of Science Core Collection (WOSCC) database and tools such as CiteSpace, VOSviewer, and R-Bibliometrix. The analysis focused on the publication volume, citation frequency, research trends, major authors, research institutions, and keywords in the hypospadias literature. The ultimate goal of this research was to pinpoint research hotspots and forecast future development trends in the field.

Data Source and Search Strategies

For our database selection, we chose the widely recognized Web of Science for our bibliometric analysis. We conducted a comprehensive search of the WOSCC database for publications related to hypospadias from January 1, 1998, to December 31, 2023. All searches were completed and downloaded on January 3, 2024, to prevent bias from daily database updates. Two authors independently verified the downloaded literature, and any disputed documents were resolved through full-text reading and discussions with corresponding authors. The search strategy used “hypospadias” as the search term, as the term “hypospadias mesh” was not found in PubMed. The inclusion criteria were limited to English-language articles or review articles. Initially, 6,078 documents were identified, with 4,525 meeting the criteria. After screening titles and abstracts, 3,647 articles that specifically focused on hypospadias were selected and imported into CiteSpace for deduplication, resulting in no duplicate documents being included, as outlined in Table 1.

Table 1: Data Screening Process.

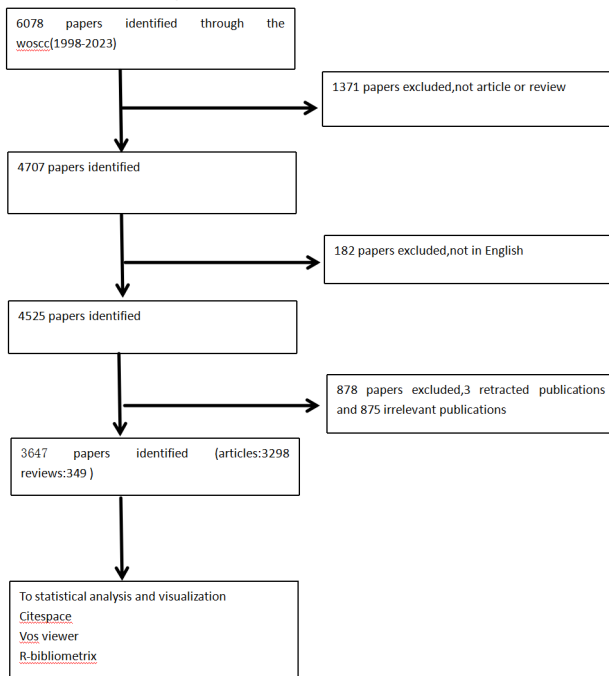


Table 2: Top Five Journals by Publication Volume.

Journal	Documents	Citations	IF (2023)	JCR (2023)
Journal of Pediatric Urology	394	4588	2	Q2
Journal of Urology	330	12208	5.9	Q1
Urology	148	2234	2.1	Q2
Pediatric Surgery International	92	993	1.5	Q2
BJU International	88	3058	3.7	Q1

Method

In the current academic landscape, there is a range of bibliometric analysis visualization software available for scholars to utilize. For the present study, we opted to use Cite Space, VOS viewer, and bibliometrix, all of which are well-established tools in the field. Cite Space, created by Dr. Chen Chaomei from the Chinese Academy of Science and Technology, is specifically designed for document co-citation analysis. We used Cite Space (version 6.2.R6) to conduct quality control measures, examine keyword prominence, and identify notable paper citations. VOS viewer (version 1.6.20) was employed to generate metrological maps based on co-occurrence data, providing visualizations in terms of networks, overlays, and densities. The visual map produced by VOS viewer uses nodes to represent various entities, including authors, journals, and keywords, with the node size indicating the frequency, line thickness denoting the connection strength, and the node color representing clusters or chronological aspects. We also employed R software and bibliometrix to monitor publication timelines and output levels of highly productive authors.

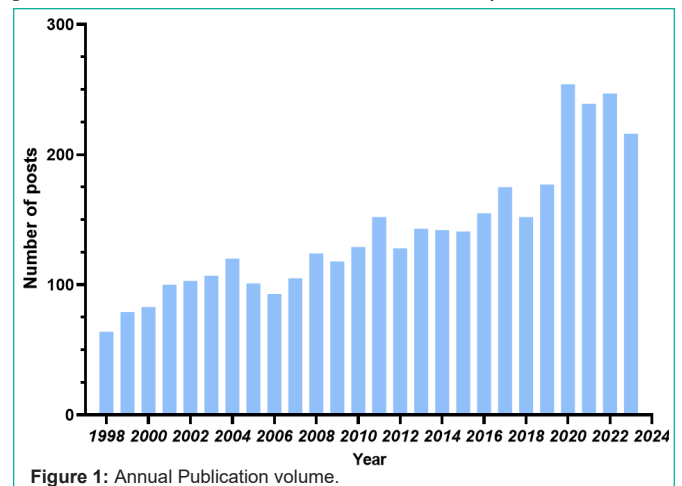
Results

Overview of Publications

The publication of scholarly articles is often regarded as a measure of advancement within a particular academic field. Fluctuations in publication rates can directly reflect shifts in the accumulation of scientific knowledge. The descriptive analysis was conducted using CiteSpace to examine the number of publications and growth trends. The study sample included 3,647 publications from 687 journals, authored by 14,633 individuals, representing 9,667 institutions across 487 countries. Among these publications, 3,298 were articles and 349 were reviews. The distribution of publications by year is illustrated in Figure 1. The annual publication count remained relatively stable from 1998 to 2016, indicating sustained interest in the field by scientists. However, there was a noticeable increase in annual publications from 2020 to 2023, exceeding 200, as well as a positive upward trend with consistent growth.

Author, Institution, and Country

Author: A total of 14,633 authors were identified in the literature search, with an average of four authors per article. The authors’ publication volume and co-citation data were analyzed and visualized



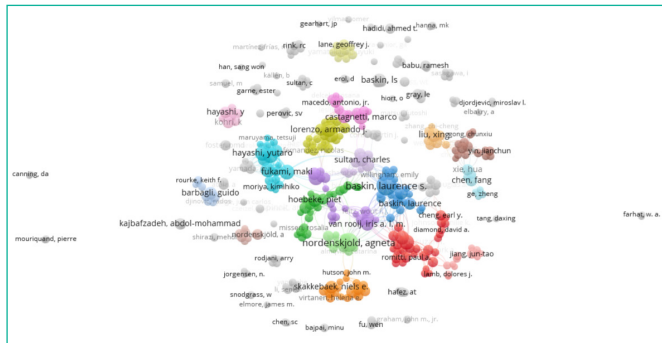


Figure 2: Author Publication Volume.

using VOS. The top five authors with the highest number of published articles were Baskin, Laurence S (38 articles), Nordenskjold, Agneta (35 articles), Snodgrass, Warren (31 articles), Fukami, Maki (22 articles), and Hayashi, Yutarō (16 articles). The top five most cited authors were Snodgrass, W (1362 times), Baskin, LS (1021 times), Duckett, JW (610 times), Carmichael, SL (407 times), and Paulozzi, LJ (407 times). According to Price’s law, the minimum number of core authors in a field is calculated as $m = 0.749 \times \sqrt{n_{max}}$, where n_{max} represents the number of papers by the most prolific authors in the field. With $n_{max} = 36$ based on Citespace statistics, m is approximately 4.49. Therefore, authors who have published five or more papers are considered core authors in the field, totaling 370 individuals. The number of core authors with ≥ 5 papers is illustrated in Figure 2, while the number of co-citations reflects the authors’ influence in the research field, as depicted in Figure 3.

We conducted a brief review of the literature published by the top five cited authors. Baskin’s research focuses on the anatomy and pathophysiology of hypospadias, as well as genetic research and advancements in surgical techniques. Nordenskjold’s study emphasizes the genetics and molecular biology of hypospadias, including the identification and functional analysis of related genes. Fukami primarily investigates the molecular mechanisms of hypospadias, particularly the association between Disorders of Sexual Development (DSD) and hypospadias. Snodgrass is renowned for developing and enhancing surgical techniques for hypospadias, notably the Snodgrass technique (also known as TIP). Hayashi delves into the surgical management of hypospadias and the assessment of long-term outcomes, encompassing postoperative complications and functional recovery.

Figure 3 illustrates the author collaboration analysis, showcasing 370 core authors who have published 5 or more papers, categorized into 74 author groups. Through an examination of the authors’ citation network, 217 authors with more than 100 citations were grouped into six author clusters (Figure 3). The connections between circles represent collaborations among authors, with the circle size indicating the number of citations. The Total Link Strength (TLS) metric reflects

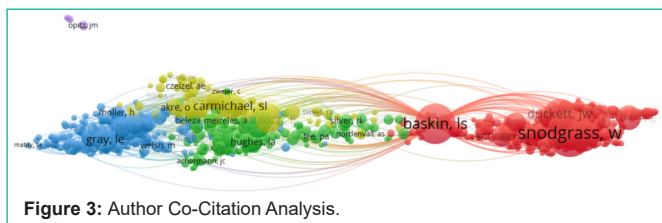


Figure 3: Author Co-Citation Analysis.



Figure 4: Publication Volume and Time Distribution of Prolific Authors.

the impact of an author’s published papers on other participating authors in the study. Notably, Baskin, Laurence S holds the highest TLS value ($n = 1645$), followed by Nordenskjold, Agneta ($n = 1093$).

R software and bibliometrix were utilized to analyze the relationship between publication time and the quantity of publications by extremely productive authors within the particular research domain, as depicted in Figure 4.

Institution: The identified documents were published by 3,537 research institutions, with 148 institutions publishing more than ten articles. The top 10 institutions collectively published 541 documents, representing 14.8% of the total publications, as depicted in Figure 5. The top three institutions in terms of published documents were the University of California, San Francisco ($n = 99$), Shanghai Jiao Tong University ($n = 67$), and the Karolinska Institute ($n = 63$). Notably, Baskin, Laurence S is a prolific scholar at the University of California, San Francisco, while Agneta Nordenskjold is a prolific scholar at the Karolinska Institute.

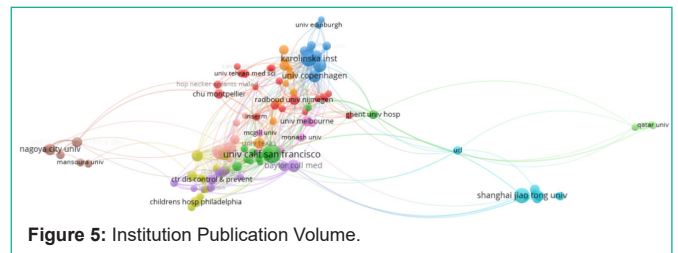


Figure 5: Institution Publication Volume.

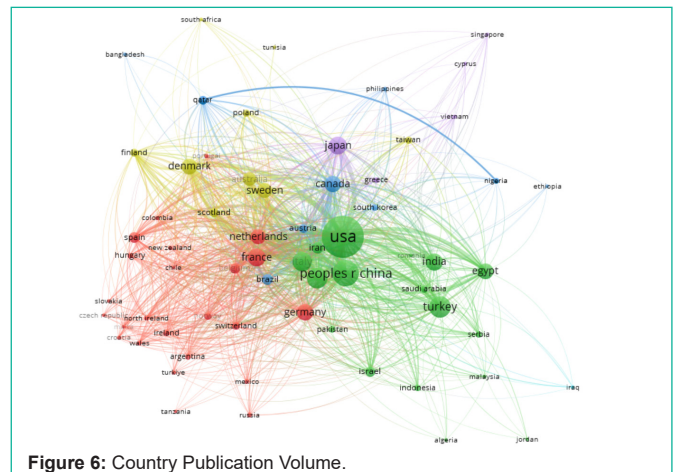
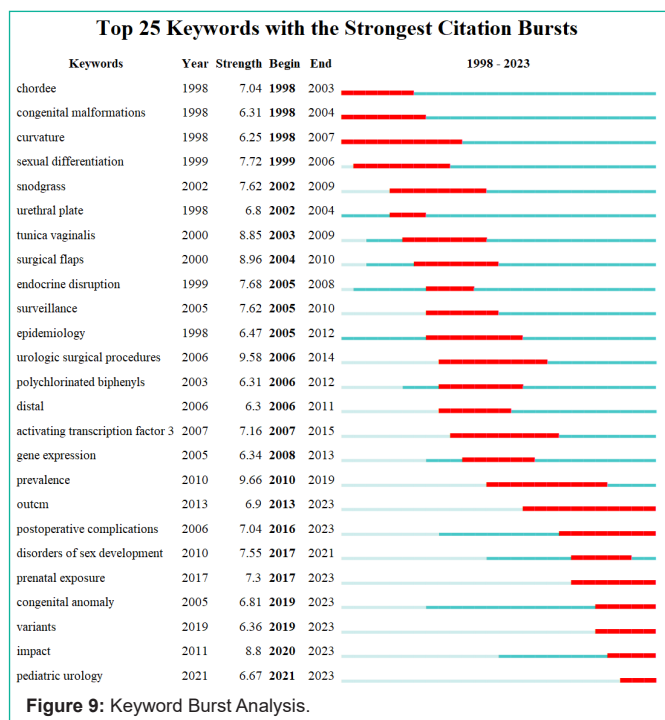


Figure 6: Country Publication Volume.



Analysis of Development Trends

In the analysis of keyword co-occurrence trends, researchers utilize time indicators to track shifts in research focus over a specific period. Visualizing keyword emergence shows that, in the past 2 decades, research on hypospadias has evolved from general clinical surgical methods to more precise flap selection and genomic studies. Advances in genetics and molecular biology have prompted a transition from enhancing surgical techniques to exploring pathogenesis, including gene identification, function, and environmental influences on hypospadias. Recent developments in gene editing, stem cell research, and tissue engineering have enabled a more precise investigation of hypospadias pathogenesis and the selection of optimal materials for urethral reconstruction, setting the stage for gene therapy and improved postoperative functional outcomes as in Figure 9.

Discussion

This study offers a concise overview of the interconnection between hypospadias, testicular agenesis syndrome, and Disorders of Sex Development (DSD). Hypospadias, Testicular Dysgenesis Syndrome (TDS), and DSD are clinical conditions characterized by developmental irregularities in the genitourinary system. Hypospadias involves an abnormal urethral opening position, TDS relates to abnormal testicular development and function, and DSD encompasses a range of sexual differentiation abnormalities. Despite their distinct characteristics, these conditions often share common molecular genetic pathways, such as disruptions in sex hormone synthesis and metabolism. Genetic variations in genes such as *SRD5A2* and *CYP17A1* can result in abnormalities in androgen synthesis and metabolism, which impact the urethra, testis, and sexual differentiation. Furthermore, variations or functional defects in the *AR* gene can lead to androgen insensitivity, influencing the development of genitalia and secondary sexual characteristics. Exposure to environmental endocrine disrupting chemicals, such as

BPA, phthalates, and PCBs, during pregnancy can disrupt fetal sex hormone synthesis, metabolism, and signaling through the placenta, thereby affecting normal reproductive system development and increasing the likelihood of hypospadias, TDS, and DSD. Patients with hypospadias and partial DSD often have mutations in genes involved in urinary tract development, such as *FOXA2* and *HOXA13*. Variations in *FOXA2* can disrupt normal urethral development, which can lead to conditions such as hypospadias. These mutations may affect the ability of *FOXA2* to regulate important downstream target genes that are essential for proper urinary tract development, including *SHH* (Sonic Hedgehog), *BMP4* (Bone Morphogenetic Protein 4), *FGF8* (Fibroblast Growth Factor 8), *PTCH1* (Patched 1), *FOXA1* (Forkhead Box A1), and *PAX2* (Paired Box 2), among others. In contrast, disorders such as TDS involve mutations in genes related to the androgen synthesis pathway, such as *SRD5A2* and *CYP17A1*. *SRD5A2* encodes an enzyme responsible for converting testosterone into Dihydrotestosterone (DHT). Mutations in *SRD5A2* can lead to decreased DHT levels, resulting in incomplete masculinization of external genitalia and conditions such as TDS. Moreover, the enzyme produced by *CYP17A1*, a member of the cytochrome P450 family 17 subfamily A, plays a critical role in androgen and steroid biosynthesis. Mutations in *CYP17A1* can disrupt androgen synthesis, potentially causing TDS and various forms of DSD. The *SRY* (sex-determining region Y) gene, located on the Y chromosome, plays a crucial role in initiating male sex determination.

Alterations or deletions of *SRY* can result in incomplete or abnormal male development, leading to DSD. The presence and proper function of *SRY* are essential for guiding testicular development, with the androgens produced by the testicles being vital for male genital development. *SOX9* (SRY-Box transcription factor 9) serves as a key regulator of male development, acting downstream of *SRY* to facilitate the differentiation of Sertoli cells in the testis. Mutations in *SOX9* can lead to conditions such as achondroplasia, which is often associated with sex reversal (46, XY DSD), underscoring its significance in sexual differentiation. The *AR* (androgen receptor) gene is responsible for encoding a receptor that specifically binds to androgens such as testosterone and dihydrotestosterone. This receptor plays a crucial role in mediating the effects of androgens in target tissues. Mutations in *AR* can cause androgen insensitivity syndrome, which is characterized by the inability of body tissues to properly respond to androgen signals. AIS can present with a spectrum of manifestations, ranging from mild hypomasculinization to more severe cases where individuals with a 46, XY karyotype experience complete feminization.

In this study, we delve into the historical evolution and advancement of hypospadias literature throughout different time periods. Prior to the 19th century, there were early descriptions and initial treatment attempts, with sporadic mentions in ancient medical texts but lacking systematic research and treatment approaches. Simple surgical procedures aimed to reconstruct the urethra, but faced challenges, with low success rates and numerous postoperative complications. From the late 19th century to the early 20th century, research primarily concentrated on improving surgical techniques, with a plethora of papers discussing the efficacy and enhancement methods of various surgical approaches. John W. Duckett's introduction of the "island flap" technique significantly enhanced surgical success rates and became the standard method in the mid

to late 20th century. Subsequently, scholars compared different surgical techniques and explored strategies to prevent and manage postoperative complications. In the 1970s, "Meatal Advancement and Glanuloplasty" were proposed for mild hypospadias. In 1994, Warren Snodgrass developed the "Tubular Incision Plate urethroplasty" (TIP), which is now widely utilized in various hypospadias repairs and is regarded as a cutting-edge technology in modern hypospadias surgery. Key research areas during this period included innovation and refinement of surgical techniques, as well as the management of complications.

By the beginning of the 21st century, advancements in genetics and molecular biology prompted a shift in research towards gene identification, functional studies, and the impact of environmental factors on hypospadias. Notable researchers, including Agneta Nordenskjold and Maki Fukami, investigated the genetic basis of hypospadias, highlighting the involvement of genes such as *CXorf6* in urethral development.

Laurence S. Baskin and his team studied the effects of environmental toxins, such as endocrine disruptors, on hypospadias occurrence, revealing the complex interplay between genetics and the environment. In the 2010s, a surge in research focused on new technologies, personalized surgical approaches, regenerative medicine, and gene therapy for treating hypospadias. Innovative technologies such as 3D printing and high-resolution imaging, along with interdisciplinary collaboration, have allowed researchers to explore the anatomical complexities of hypospadias and develop personalized surgical strategies. Moreover, progress in stem cell and tissue engineering has advanced regenerative medicine for hypospadias, with ongoing studies on the use of stem cells to regenerate urinary tract tissues for improved function. Additionally, the emergence of gene editing tools such as CRISPR/Cas9 has provided researchers with new insights into the causes of hypospadias in animal models, highlighting the potential of gene therapy in this field.

Conclusion

This study has some limitations. First, the deadline for the analyzed publications was December 31, 2023, but the WOSCC data are continuously updated. Therefore, the gathered literature may not capture the latest developments in 2024, while the older literature may have incomplete data. Second, contributions from non-English literature may have been overlooked due to language selection restrictions. Despite these limitations, the study is significant as it systematically summarizes the knowledge structure and research frontiers of hypospadias research using bibliometrics and visual analysis. This report highlights new research hotspots and directions, indicating future breakthroughs in research and treatment with advancements in 3D printing, stem cell technology, and gene editing. Personalized treatment strategies targeting specific genetic variants are expected to improve efficacy and reduce complications. Furthermore, understanding the effects of environmental pollutants on sex hormone synthesis and signaling will lead to the development of public health strategies to mitigate exposure to endocrine disruptors, thereby improving the current scenario. Future research should focus on individualized treatment and effective prevention methods to enhance overall understanding of trends in the field.

Author Statements

Data Availability Statement

Web of science.

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Declaration of Competing Interest

The authors have no actual or potential competing interest related to this manuscript.

CRedit Authorship Contribution Statement

All authors read, critically reviewed, and approved the final manuscript. Dezhi Su and Guomin Zhai designed the research; Sha Li and Kun Wang: collected the data; Gangquan Wu: recheck the data; Writing – original draft. Guomin Zhai: Writing – original draft. Xiaowei Li: Writing – review, Funding acquisition. Dezhi Su and Guomin Zhai: Writing – review & editing, Conceptualization.

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