Submitted: 30 November, 2025 Accepted: 20 January, 2026 Published: 30 June, 2026 DOI:10.22514/jomh.2026.052

ORIGINAL RESEARCH

JOMH Journal of Men's Health

Bibliometric and scientometric analysis of late-onset hypogonadism in the past two decades: knowledge mapping and research trends

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Abstract

Background: Late-onset hypogonadism (LOH) is a clinical biochemical and clinical syndrome characterized by testosterone decline in association with increasing age. LOH prevalence is expected to increase further given the rapidly aging global population, and become a significant health burden. The present study employed bibliometric and scientometric analysis to present a comprehensive overview of the global research landscape on LOH. **Methods**: We searched for publications on LOH published between 2002 and 2024 in the Web of Science Core Collection database. Using Bibliometrix, VOSviewer, and CiteSpace, we conducted bibliometric analysis and visualization. **Results**: Totally, 1561 publications were included in this study. The annual publications generally remained on an upward trend with an annual growth rate of 4.06%. The most prolific journal, country, institution, and author was Aging Male, the United States, University of Florence, and Maggi M, respectively. The economic status affects scientific research output. Multinational collaboration was more common in Europe and North America, and in high income countries. The keyword burst analysis demonstrated the representative burst keywords were "testosterone replacement therapy" (TRT) and "Leydig cells". The terminology use analysis in the titles of the publication showed that "LOH" was the most popular terminology (50.2%), followed by "andropause" (22.8%) and "androgen/testosterone deficiency syndrome" (10.8%). In the LOH field, most research focused on clinical studies (86.9%), and there was only a small proportion of experimental studies (13.1%). **Conclusions**: Overall, this bibliometric and scientometric analysis provided a comprehensive overview of LOH and yielded quantitative and qualitative insights. The study identified the most prominent publications, journals, countries, institutions and authors in LOH research. The Keyword burst analysis demonstrates the latest research trends and hotspots ("TRT" and "Leydig cells"). Future studies should emphasize the establishment of an optimal and unified terminology, along with the promotion of experimental studies.

Keywords

Late-onset hypogonadism; Aging male; Male hypogonadism; Bibliometric analysis; Research trends

1. Introduction

Late-onset hypogonadism (LOH) is a clinical and biochemical syndrome associated with aging, and is characterized by typical symptoms and low testosterone concentration [1, 2]. The total testosterone in men after reaching 40 years declines at an average rate of 0.8% to 1.6% per year [3, 4]. Hence, LOH prevalence increases with aging. In men aged 40–79 years, LOH prevalence varies between 2.1% and 25.6% [5]. Moreover, given a rapid aging global population, the prevalence is expected to further rise, and the burden of LOH is becoming a significant challenge [1].

LOH can manifest a range of clinical signs and symptoms depending on disease severity and age of onset, such as general malaise, fatigue, sexual dysfunctions, depressive mood, and decreased bone density [1–3]. These signs and symptoms frequently lead to a significant reduction in the quality of life (QoL). In clinical practice, the mechanism and diagnostic criteria of LOH remain incompletely clarified. LOH can be caused by primary and/or secondary impairment of the hypothalamic-pituitary-testicular axis [6]. Furthermore, people with metabolic syndrome, which encompasses obesity, type 2 diabetes and hyperlipidemia, have a higher risk of LOH [2]. Moreover, smoking and alcohol and drug use can

contribute to LOH development. The biochemical threshold for diagnosing LOH is widely considered to be 12 nmol/L. Once LOH is diagnosed, the patient should first treat the LOH-related risk factors; if that is unsuccessful, then testosterone replacement therapy (TRT) needs to be taken into consideration. Clearly, a comprehensive overview and analysis of research trends in LOH could provide valuable insights and guidance for researchers exploring diverse facets within this domain.

Bibliometric and scientometric research is a research technology, that can present a quantitative overview of the research field [7–9]. It has more advantages than traditional reviews as it aids more intuitive and vivid understanding of the research. Furthermore, it can identify potential research directions and create a road map for further exploration. Currently, there are a large number of LOH publications. However, no studies have analyzed LOH using bibliometric methods. Accordingly, the present study conducted a bibliometric analysis of LOH research.

2. Materials and methods

2.1 Data acquisition and search strategy

We conducted a literature search of the Web of Science Core Collection (WoSCC) database in July 2024, including Science Citation Index Expanded (SCI-EXPANDED, 1900–present), Social Sciences Citation Index (SSCI, 1900–present), Arts & Humanities Citation Index (AHCI, 1975–present), Conference Proceedings Citation Index-Science (CPCI-S, 1990–present), Conference Proceedings Citation Index-Social Science & Humanities (CPCI-SSH, 1990–present), Emerging Sources Citation Index (ESCI, 2019–present), Current Chemical Reactions (CCR-EXPANDED, 1985–present) and Index Chemicus (IC, 1993–present). The WoSCC is a comprehensive academic literature citation database, created and maintained by Clarivate Analytics. The database hosts high-quality academic publications from all disciplines.

LOH-related scientific publications were searched based on the "Topic" field. Two comprehensive search strategies were developed to enable a thorough and accurate search (**Supplementary material 1**). The search strategy was established using "LOH" and its synonymous terms. The publication type was restricted to articles and reviews. The document language was restricted to English. Finally, we included documents published from 2002 to 2024. The titles of the documents retrieved based on search strategy 2 were manually screened first in order to remove irrelevant publications.

2.2 Data analysis

The final dataset in the BibTeX, tab delimited, and plain text formats was imported into Bibliometrix, VOSviewer, and CiteSpace, respectively. The main information from the documents included in this study were extracted using Bibliometrix R package [10]. The main analyses and visualization, such as co-operation, citation, co-citation, co-occurrence networks, were conducted using VOSviewer (1.6.20, Nees Jan van Eck, Leiden, Netherlands) [11]. Keyword burstiness analysis was conducted using CiteSpace 6.4.R1 (Advanced, Chaomei Chen, Philadelphia, PA, USA) [8]. Lastly, graphs were plotted using GraphPad Prism 10 (GraphPad Software, Boston, MA, USA).

3. Results

3.1 Productivity analysis

Our dataset initially retrieved 2166 documents. Data quality control and filtering excluded 605 (27.9%) documents (Fig. 1). Finally, a total of 1561 documents (1161 articles, 400 reviews) and a cumulative 40,471 references were retained (**Supplementary Table 1**). Among the 1161 articles, clinical and experimental studies shared 86.9% (n = 1009) and 13.1% (n = 152), respectively. Fig. 2A illustrates a generally stable increase in annual publications with an annual growth rate of 4.06%, particularly in the year 2016, which peaked at 113 publications. The average citations per document were 31.74, and the average citations per year mainly fluctuated between two and four except in 2010, where the average citations were 6.3 (Fig. 2A). These findings underscored the increasing research interest in LOH.

3.2 Terminology analysis

LOH is a clinical biochemical and clinical syndrome characterized by testosterone decline in association with increasing age. The "aging male syndrome" concept, however, is anything but new [12–15]. Several names have been proposed for this syndrome. Table 1 lists the different terminologies for testosterone deficiency in the adult male. Henry Halford coined the term "climacteric disease" in males in 1813 [15]. "Male climacteric" and "male menopause" have been discussed since the 1930s. In 2006, Morales *et al*. [14] proposed the term "testosterone deficiency syndrome" (TDS) as the optimal name. Currently, the most popular and widespread term is "LOH", proposed in 2002. Nevertheless, the somewhat confusing use of the above terminology in the clinical setting persists.

The terminology use was analyzed by manually checking the titles of the 1561 publications. Among those, 416 documents used one of the terminologies listed in Table 1 in the title. Most titles used "LOH" (50.2%), followed by "andropause" (22.8%) and "androgen/testosterone deficiency syndrome" (ADS/TDS, 10.8%) (Fig. 2B). Fig. 2C depicts the annual percentage distribution of the terminology. Similar to the results in Fig. 2B, "LOH" was the most frequently used terminology. Since 2007, "LOH" was used in $\geq$50% of titles except in 2012, 2013 and 2018. "Androgen decline in the aging male" (ADAM), "partial ADAM" (PADAM), "male climacteric" and "male menopause" were used sporadically, especially in recent years. Even the term "ADS/TDS", which some experts consider the most accurate, was not commonly used after 2015 [14]. More recently, the newer and widely recommended term that has been coined for LOH is functional hypogonadism in middle-aged and elderly males (not shown in Table 1 and Fig. 2) [16].

3.3 Analysis of journals

The 1561 publications on the topic were distributed among 480 journals indexed in WoSCC, six of which had >30 publications (**Supplementary Table 2**). Nearly one third of the total

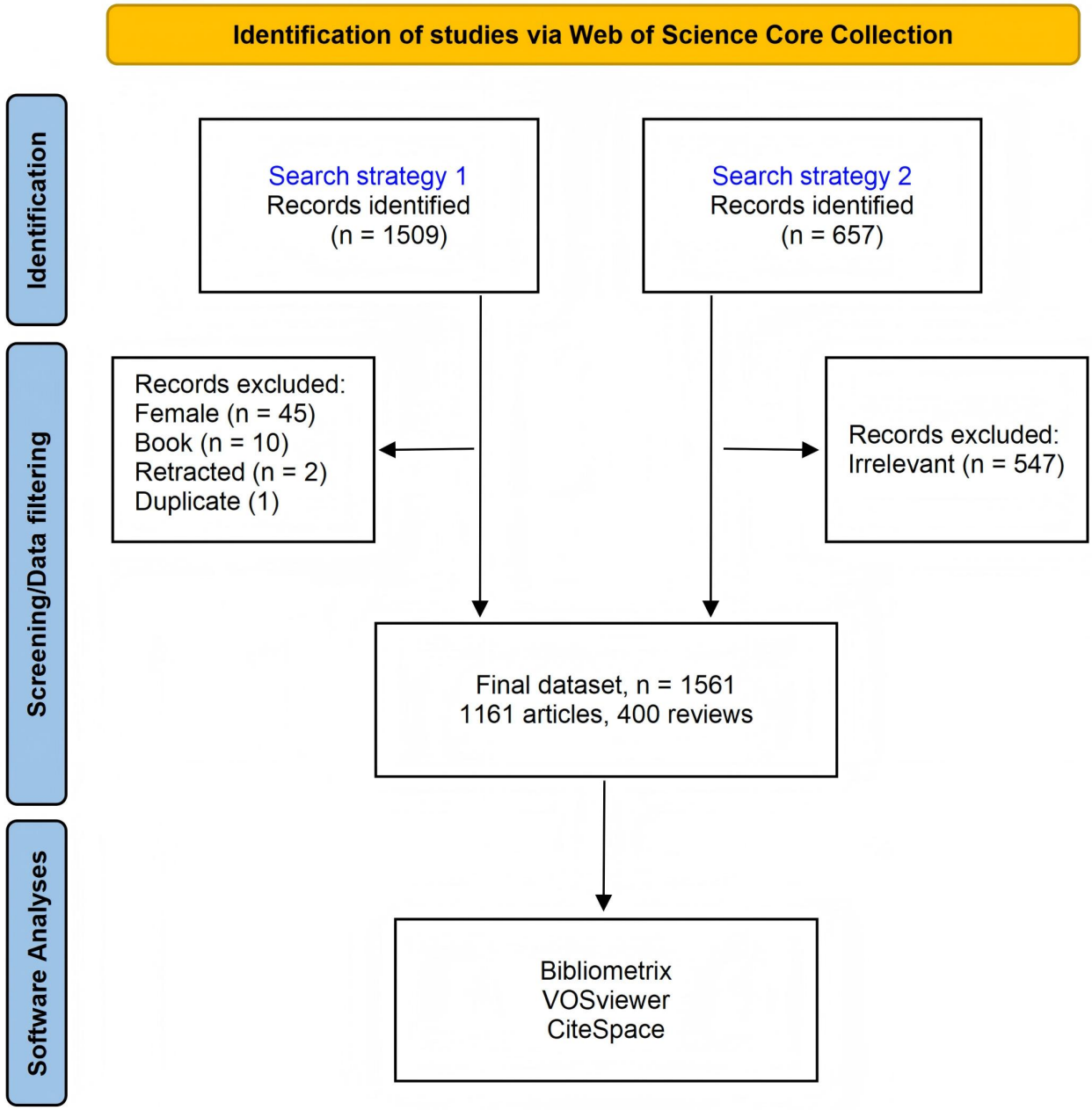

FIGURE 1. Flow chart of the scientometric study. Search strategies can be found in the **Supplementary material**.

TABLE 1. Terminology for testosterone deficiency in the adult male.

Terminology	Percentage (%)	Coined/Proposed time
Climacteric disease	NA	1813
Male climacteric	2.9	1930s
Male menopause	2.2	1930s
Andropause	22.8	1987
Androgen deficiency in the aging male	3.6	1994
Partial androgen deficiency in the aging male	5.3	1994
Late-onset hypogonadism	50.2	2002
Androgen/testosterone deficiency syndrome	10.8	2006
Adult-onset hypogonadism	2.2	2015

NA: not available.

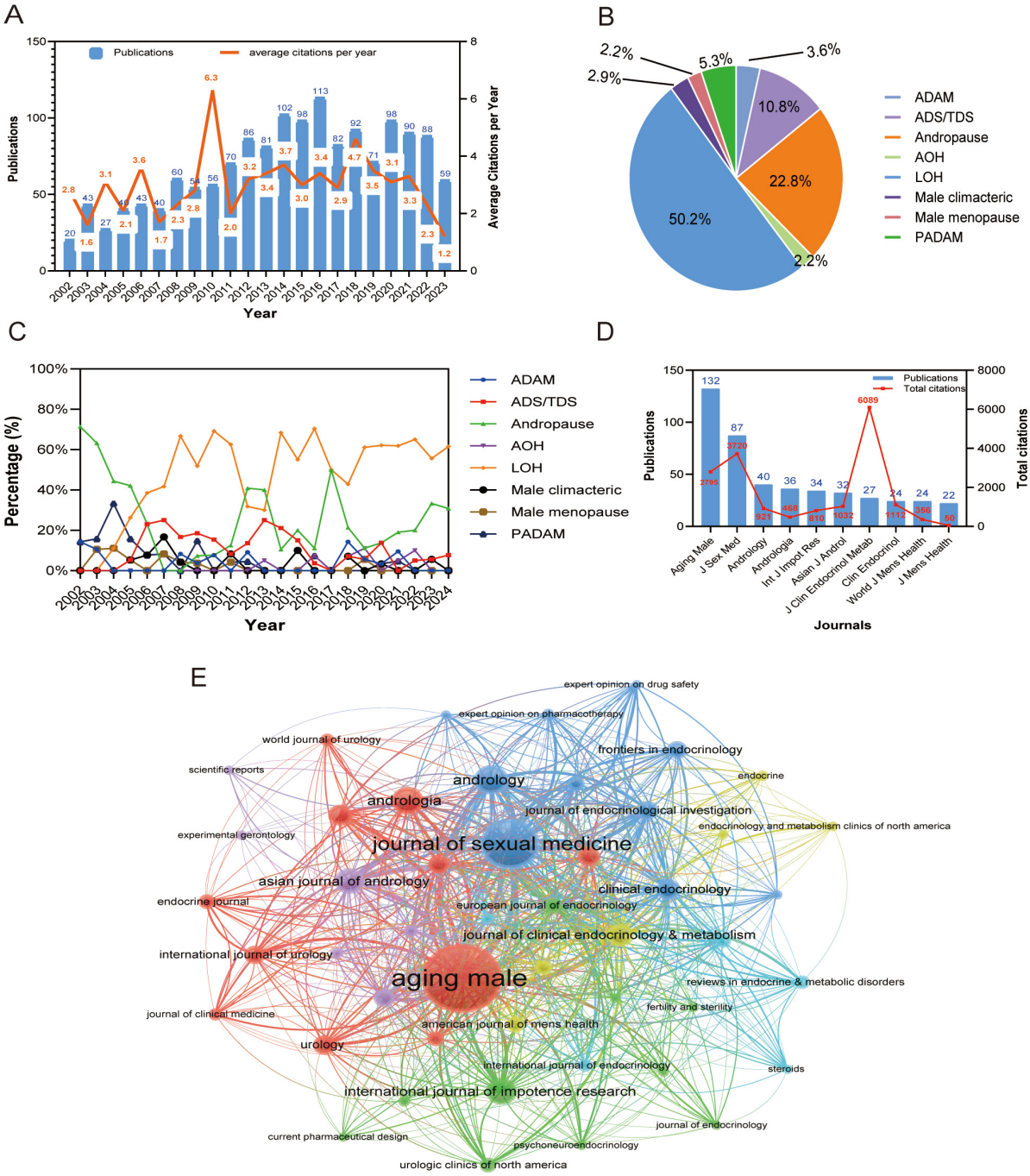

FIGURE 2. Analysis of productivity, terminology and journals. (A) Annual publications and average citations per year (mean citations per year per document); (B) Terminology usage percentage in publication title; (C) Annual usage percentage of terminology; (D) Top 10 journals with the most publications; (E) Citation network map of 48 journals. ADAM: androgen decline in the aging male; ADS: androgen deficiency syndrome; TDS: testosterone deficiency syndrome; AOH: adult-onset hypogonadism; LOH: late-onset hypogonadism; PADAM: partial ADAM.

documents were published in the top 10 journals (n = 458, 29.3%). The top 5 journals are the Aging Male (n = 132, 8.5%), Journal of Sexual Medicine (n = 87, 5.6%), Andrology (n = 40, 2.6%), Andrologia (n = 36, 2.3%), and International Journal of Impotence Research (n = 34, 2.2%) (Fig. 2D). **Supplementary Table 3** lists the top 10 most cited journals.

Additionally, a journal citation network map was developed, with each journal having at least 5 publications and 100 citations. Totally, 48 of the 480 journals were included in the network map (Fig. 2E). Among those, Journal of Clinical Endocrinology & Metabolism, Journal of Sexual Medicine, and the Aging Male were the top 3 influential journals, with citations totaling 6089, 3720, and 2795, respectively (**Supplementary Table 3**). The New England Journal of Medicine had the highest average citations, and Journal of Sexual Medicine had the highest H-index with 35. Taken together, these results can aid researchers in identifying the most suitable journals to which to submit their LOH research manuscripts.

3.4 Analysis of countries

Out of the 1561 publications, 74 countries contributed to the LOH discipline in total with a high geographical concentration. **Supplementary Table 4** shows the top 10 most prolific countries. Among the 74 countries, the United States produced the most publications (n = 422, 27.0%), followed by Italy (n = 227, 14.5%), the United Kingdom (n = 145, 9.3%), China (n = 139, 8.9%), and Japan (n = 139, 8.9%) (Fig. 3A). In addition, the publication production on LOH by country regarding the economy, in accordance with the World Bank and the United Nations population division, was also analyzed [17]. As shown in Fig. 3B, the high-income (HI) countries contribute the most publications to the LOH field (83.5%), followed by the upper-middle income (UMI) countries (13.6%), lower-middle income (LMI) countries (2.9%) and low-income (LI) countries (0.05%).

Fig. 3C displays the overlay visualization map of co-authorship between countries (at least 5 publications and 1 citation). These countries were grouped into five major clusters (**Supplementary Table 5**), and each cluster was predominated by one or two main countries. Notably, the United States, Italy, China, Germany, and the United Kingdom regularly collaborated with other countries. Asian countries such as China and Korea recently collaborated with other countries more frequently.

3.5 Analysis of institutions

A total of 1098 institutions were identified in the LOH field. Table 2 lists the top 10 most prolific institutions. Unsurprisingly, the University of Florence produced the most publications (n = 103, 6.6%), followed by AUSL di Bologna (n = 79, 5.1%) and University of California System (n = 53, 3.4%) (Fig. 4A). The top 10 most prolific institutions were in the developed countries and were mostly in Europe and North America. Furthermore, collaborations between different institutions were analyzed. Regarding the total number of

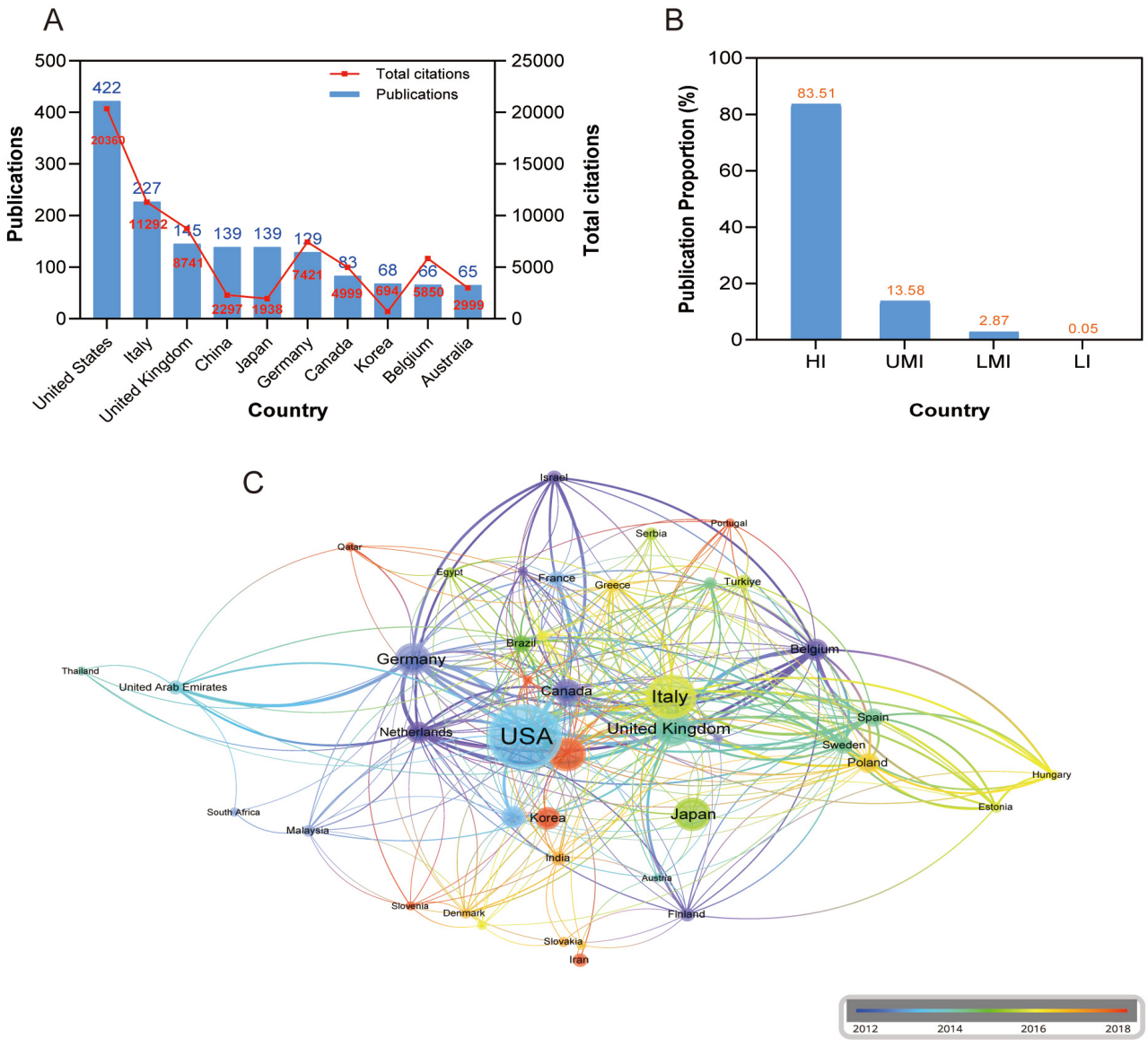

FIGURE 3. Analysis of countries. (A) Top 10 countries with the most publications; (B) Publication percentage stratified by country regarding the economy; (C) Cooperation network map of countries. HI: high-income; UMI: upper-middle income; LMI: lower-middle income; LI: low-income.

TABLE 2. Top 10 most prolific organizations.

Ranking	Organization	Original country	Publications	Percentage (%)	Total citations	Average citations
1	University of Florence	Italy	103	6.6	7492	72.7
2	AUSL di Bologna	Italy	79	5.1	4391	55.6
3	University of California system	United States	53	3.4	6053	114.2
4	Baylor College of Medicine	United States	52	3.3	4992	96.0
5	Harvard University	United States	51	3.3	3936	77.2
6	Sapienza University Rome	Italy	48	3.1	2265	47.2
7	University of Manchester	United Kingdom	42	2.7	5337	127.1
8	Geriatric Research Education & Clinical Center	United States	37	2.4	3133	84.7
9	Vrije Universiteit Amsterdam	Netherlands	37	2.4	2777	75.1
10	Imperial College London	United Kingdom	35	2.2	3547	101.3

citations, University of Florence, University of California System, and University of Manchester were the top 3 influential institutions, with citations totaling 7492, 6053, and 5337, respectively (Table 2, Fig. 4A).

The graph in Fig. 4B depicts the network map of collaborating institutions. Ten clusters were identified, each with at least 5 publications and 100 citations (highlighted in different colors). Among the five main clusters, Harvard University, University of Manchester, University of Florence, University of London, and Geriatric Research Education & Clinical Center frequently collaborated with other institutions.

3.6 Analysis of authors

Totally, 5414 authors were identified among the 1561 publications. Fig. 4C and **Supplementary Table 6** show the top 10 most productive authors. Of them, Maggi M (n = 91, 5.8%) from the University of Florence was the most productive author, followed by Corona G (n = 78, 5.0%, University of Florence), Rastrelli G (n = 54, 3.5%, University of Florence), Saad F (n = 29, 1.9%, Bayer AG), and Wu FCW (n = 28, 1.8%, University of Manchester). Six of the 10 most productive authors were from Italy, suggesting that Italy has made significant academic contributions to the development of the LOH field. Interestingly, the 10 authors who published the most documents were involved in the same study: the well-known European Male Aging Study (EMAS), a multi-center study involving many researchers in different European countries [18]. The study aimed to examine the body composition and symptoms of aging men of various ages from various regions to achieve the goal of extending the male lifespan (see below).

Fig. 4D illustrates the network map of co-authorship and collaboration (at least 5 publications and 100 citations). These authors were grouped into eight major clusters (highlighted in different colors), and each cluster was predominated by one or two main authors, such as Maggi M, Corona G, Wu FCW, and Morales A. As highlighted in red, some authors such as Antonio L, Giagulli VA, and Ramachandran S have showed an increasing interest in the LOH field and collaborated with other authors more frequently in recent years.

3.7 Analysis of highly cited articles and co-cited references

Citation analysis serves as a useful method to assess the degree of relationship between documents. The citation analysis was performed, and Table 3 presents the top 10 most frequently cited publications: five reviews and five articles. No experimental studies were identified. Six of the top 10 publications were published in Journal of Clinical Endocrinology and Metabolism, which also had the highest number of citations (**Supplementary Table 3**). Three documents were published in 2010, thus partially explained the high average citations per document in this year (Fig. 2A). The top-ranked publication was authored by Bhasin S (2010), which was a clinical practice guideline and discussed "testosterone therapy in men with androgen deficiency syndromes" with a total citation of 1421. We also analyzed the top 10 most frequently co-cited references (**Supplementary Table 7**), where the frequently co-cited references were Wu FCW (2010), Harman SM (2001), and Bhasin S (2010).

3.8 Analysis of author keywords

We merged the synonymous keywords and performed a keyword co-occurrence analysis. Given their representativeness, the author keywords were selected for the analysis. **Supplementary Table 8** shows the top 20 most common keywords from 2002 to 2024. Among those, "testosterone" (633 occurrences) was the most frequently occurring keyword, followed by "LOH", "hypogonadism", "TRT", and "aging". Fig. 5A depicts the overlay visualization map created using 144 keywords with at least 5 occurrences. The keywords that appeared early are highlighted in blue, while recently occurring keywords are highlighted in red. The map indicates that the "Leydig cells", "selective estrogen receptor modulator", "functional hypogonadism", "senescence", and "replacement therapy" research directions are recent hot topics of great interest.

Based on the keyword co-occurrence analysis, a citation burst analysis was performed. The top 6 intensely cited keywords related to LOH are extracted. In Fig. 5B, the light

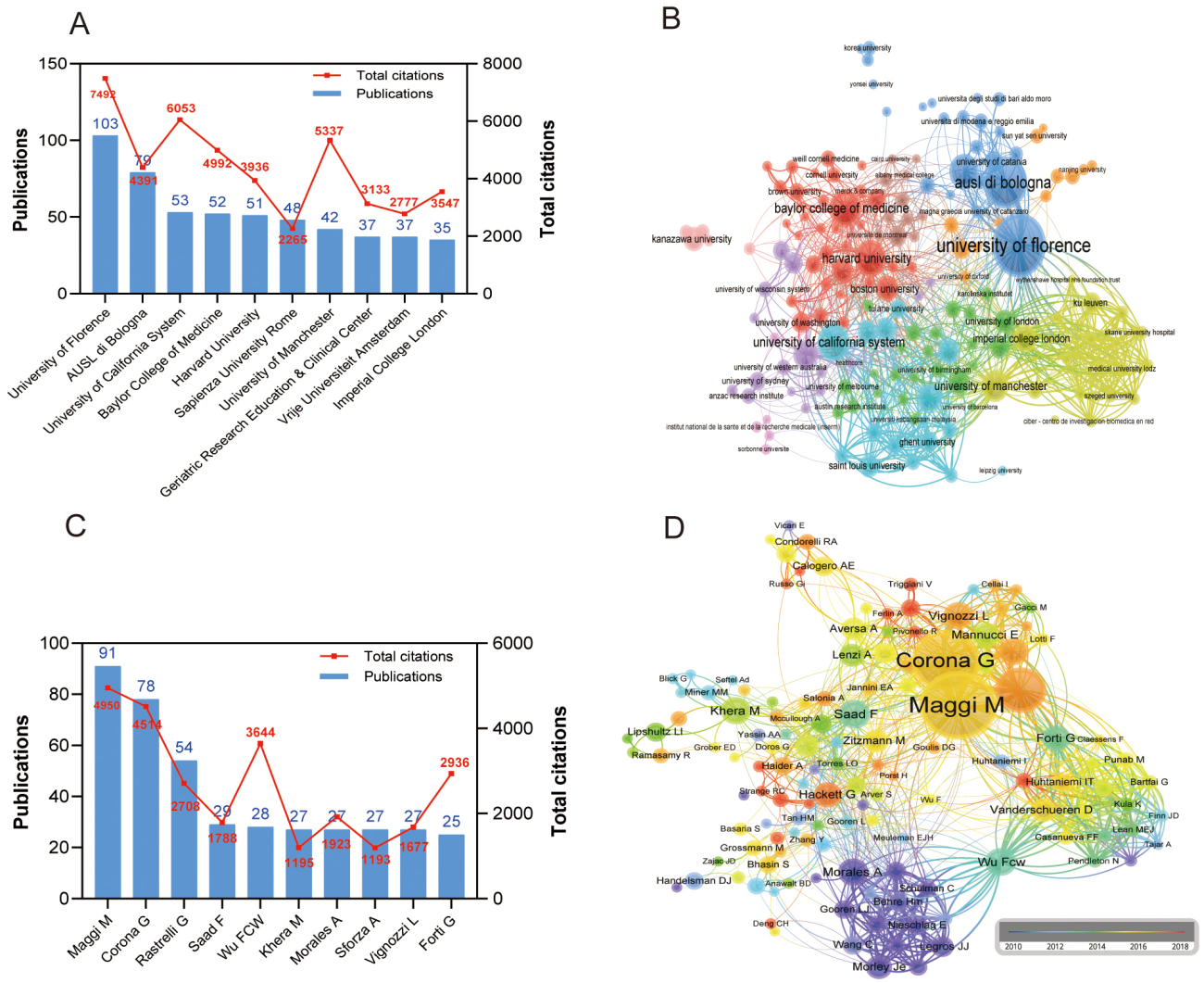

FIGURE 4. Analysis of institutions and authors. (A) Top 10 institutions with the most publications; (B) Cooperation network map of 44 institutions; (C) Top 10 authors with the most publications; (D) Cooperation network map of authors.

TABLE 3. Top 10 publications with highest citations.

Ranking	Total citations	First author	Title	Type	Source
1	1421	Bhasin S (2010)	Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline	review/guideline	J Clin Endocrinol Metab
2	984	Wu F C (2010)	Identification of late-onset hypogonadism in middle-aged and elderly men	article/clinical	N Engl J Med
3	907	Bhasin S (2018)	Testosterone therapy in men with hypogonadism: an Endocrine Society clinical practice guideline	review/guideline	J Clin Endocrinol Metab
4	678	Bhasin S (2006)	Testosterone therapy in adult men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline	review/guidelin	J Clin Endocrinol Metab
5	428	Araujo A B (2004)	Prevalence and incidence of androgen deficiency in middle-aged and older men: estimates from the Massachusetts Male Aging Study	article/clinical	J Clin Endocrinol Metab
6	419	Tajar A (2010)	Characteristics of secondary, primary, and compensated hypogonadism in aging men: evidence from the European Male Ageing Study	article/clinical	J Clin Endocrinol Metab

TABLE 3. Continued.

Ranking	Total citations	First author	Title	Type	Source
7	418	Xu L (2013)	Testosterone therapy and cardiovascular events among men: a systematic review and meta-analysis of placebo-controlled randomized trials	review	BMC Med
8	395	Emmelot-Vonk M H (2008)	Effect of testosterone supplementation on functional mobility, cognition, and other parameters in older men: a randomized controlled trial	article/clinical	JAMA
9	377	Zitzmann M (2006)	Association of specific symptoms and metabolic risks with serum testosterone in older men	article/clinical	J Clin Endocrinol Metab
10	356	Wang C (2008)	Investigation, treatment and monitoring of late-onset hypogonadism in males: ISA, ISSAM, EAU, EAA and ASA recommendations	review	Eur J Endocrinol

ISSAM: International Society for Sexual Medicine; ISA: International Society of Andrology; EAU: European Association of Urology; EAA: European Academy of Andrology; ASA: American Society of Andrology.

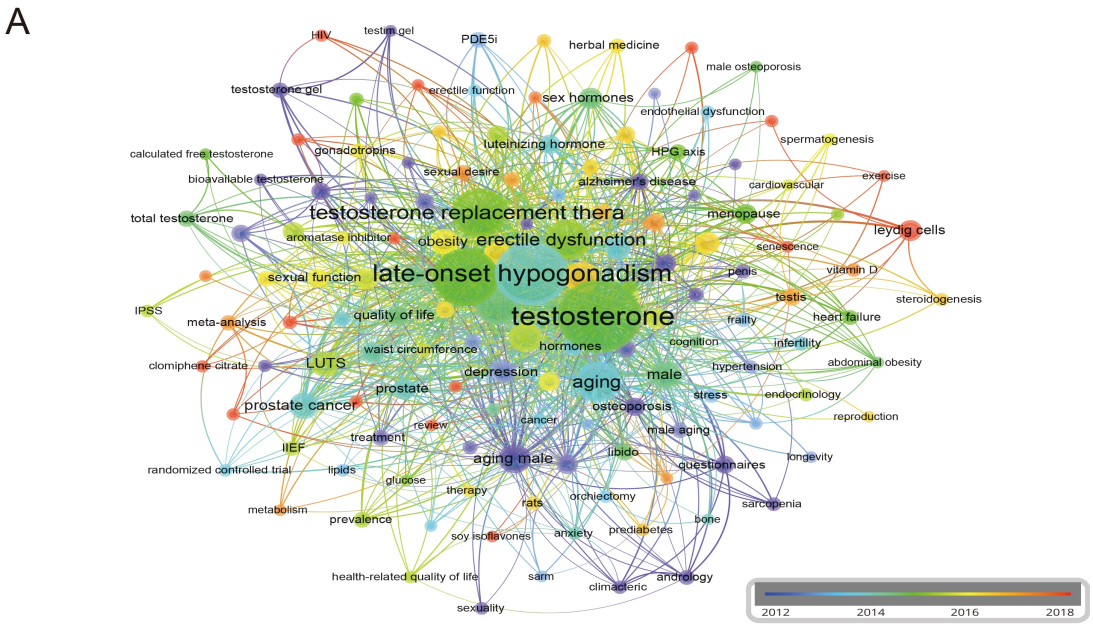

FIGURE 5. Analysis of author keywords. (A) Network map of the authors' keywords; (B) Citation burst analysis of the authors' keywords. HIV: human immunodeficiency virus; PDE5i: phosphodiesterase-5 inhibitor; IPSS: International Prostate Symptom Score; LUTS: lower urinary tract symptoms.

blue line represents the time axis, while the red line represents the beginning and ending year of the burst (burst duration). Generally, a greater the increase of keywords cited in this period denoted higher strength. "Aging male" had the strongest citation bursts (strength = 8.17), followed by "Leydig cells" (strength = 4.57) and "testosterone undecanoate" (TU, strength = 4.27).

4. Discussion

4.1 General information

This bibliometric and scientometric analysis presents a comprehensive overview on LOH, providing both quantitative and qualitative insights. It helps researchers identify the most prominent publications, journals, countries, institutions and authors, as well as the latest research trends and hotspots. This study included 1561 documents published between 2002 and 2024, where publication peaked in 2016 with 113 documents. Around 2013–2015, a vigorous academic debate emerged concerning TRT and associated safety concerns, particularly regarding cardiovascular risks [19]. This discourse prompted the United States Food and Drug Administration (FDA) to issue safety communications [20, 21]. These events likely led to the surge in publications and citations in 2016 as researchers explored the risks. Regarding the scientific production, the annual publications generally remained on an upward trend with an annual growth rate of 4.06%. The results revealed a constant research interest in LOH in recent years.

With respect to the journals, a total of 480 journals were found. The most influential journal with the highest citations was Journal of Clinical Endocrinology & Metabolism (6089 citations), followed by Journal of Sexual Medicine (3720 citations) and Aging Male (2795 citations). Journal of Clinical Endocrinology & Metabolism is one of the foremost journals worldwide focusing on the clinical practice of endocrinology, diabetes, and metabolism. Journal of Sexual Medicine is the official journal of the International Society for Sexual Medicine (ISSM) and the International Society for the Study of Women's Sexual Health. The journal focuses on foundational scientific and clinical research on the psychological and biological aspects of male and female sexual function and dysfunction. Aging Male is the official journal of the International Society for the Study of the Aging Male (ISSAM). The journal primarily encompasses studies related to male health throughout the aging process. LOH is an age-related clinical and biochemical syndrome associated, and these 3 journals partially reflects the three aspects of LOH: aging, hormones and sexual function. These findings highlighted the fundamental role of these journals in promoting and disseminating studies on LOH.

As for the cooperation, we analyzed the cooperation networks of countries, institutions and authors. The top 3 most prolific countries were the United States (n = 422, 27.0%), Italy (n = 227, 14.5%) and the United Kingdom (n = 145, 9.3%), which have prominently influenced LOH research development and progress. No doubt, the economic status affects its scientific research output. In the present study, nearly three quarters of publications (83.5%) were produced by the HI countries, suggesting some gaps between countries with different incomes. Not surprisingly, the United States, Italy, Germany, and the United Kingdom regularly collaborated with other countries. Encouragingly, some non-HI countries such as China (UMI) and India (LMI) recently published more articles and collaborated with other countries more frequently. Regarding the institutions and authors with the highest scientific production, similar results were found. Most of the top 10 most prolific institutions/authors were from Europe and North America, and from HI countries. The University of Florence produced the most publications (n = 103, 6.6%), followed by AUSL di Bologna (n = 79, 5.1%) and University of California System (n = 53, 3.4%). Among the authors, Maggi M (n = 91, 5.8%) from the University of Florence was the most productive author, followed by Corona G (n = 78, 5.0%, University of Florence), Rastrelli G (n = 54, 3.5%, University of Florence), Saad F (n = 29, 1.9%, Bayer AG), and Wu FCW (n = 28, 1.8%, University of Manchester). These authors are in leading position in this field.

Multinational collaboration in LOH research is gaining increasing attention. To date, several multinational studies on LOH were conducted, among which the EMAS is one of the most well-known [22]. It is a multicenter prospective cohort study conducted in eight European countries aiming to determine the prevalence, incidence, and geographical distribution of symptoms of ageing in males (40–79 years). Totally, it recruited 3369 men (mean age of 60 $\pm$ 11 years) and has achieved significant results, from which numerous articles have been published [18]. The researchers determined that $>$50% of the participants had at least one common morbidity, of which the top three were hypertension, obesity and heart diseases. Approximately 30% of participants reported erectile dysfunction, related to aging and concomitant morbidities. Males in emergent countries reported a higher incidence rate and higher likelihood of sexual dysfunction, and a lower QoL. The research group concluded that sexual health declined with aging in European men, and the risk of concomitant morbidities increased [23].

4.2 Naming of LOH using unified terminology

With aging, there is a decline in testosterone production [14]. Researchers have well recognized and widely documented this condition clinically for a long time [13–15]. An assortment of names has been designated to describe the condition, reflecting a variety of opinions (Table 1). The term "LOH" was first used officially in a lecture at the 17th Congress of the Polish Endocrine Society on 26 May in 2002 [24]. In the same year, LOH was discussed at the 10th World Congress on the Menopause on 02 June, and it was recommended to name the deficiency in testosterone production. In 2006, Morales A *et al*. [14] proposed the term "TDS" and submitted that TDS was the best option. More recently, the Sexual Medicine Society of North America (SMSNA) coined "adult-onset hypogonadism" (AOH) in 2015 [25]. Although LOH was proposed for over 2 decades, it currently remains the most popular terminology at present. LOH shared the highest proportion of publications (50.2%). However, in other words, the other 50% of

the publications used other synonymous terminologies, such as ADAM, PADAM, and TDS. Unfortunately, there was no remarkable decrease in using different terms even in the last 5 years (Fig. 2C). Using unified and standard terminology, undoubtedly, will convey conceptual clarity and rational basis for disease management, particularly for information retrieval and dissemination. Therefore, the results of terminology analysis in this study highlighted the need for an optimal and unified terminology.

4.3 Hotspots and frontiers

Keyword burst analysis can provide insight into changes in research hotspots, as well as predict future trends in research. In the present study, the keyword burst analysis demonstrated the representative burst keywords were "aging male" (2002–2005), "TU" (2003–2013), "Alzheimer's disease" (2004–2008), "testosterone gel" (2012–2013), "QoL" (2017–2018), and "Leydig cells" (2020–2024).

4.3.1 TU

TRT is now the most common medical approach for LOH patients who are not interested in fathering [26]. TRTs begin in the 1940s, although earlier therapies are not considered to be optimal by current practice [27]. Kinds of pharmacological therapies exist, and TU is currently considered a very promising treatment modality. As one of the testosterone esters, TU (3-oxoandrost-4-en-17-yl undecanoate) is an 11-carbon derivative which is prepared by esterification of natural testosterone at the 17-β position with undecanoic acid. Compared to traditional testosterone esters, for instance, testosterone enanthate and testosterone cypionate, TU has considerable long-term kinetics, allowing for longer dosing intervals [26, 28]. Many exogenous testosterone formulations are available, such as oral, parenteral, transmucosal, and subdermal. Testosterone esters were first developed in the 1950s [27]. TU comes in an oral or injectable formulation, and it is currently the only available oral formulation for TRT (Table 4). The oral administration is typically the most convenient route with the following advantages: (1) convenient administration; (2) flexible dosage adjustment; (3) suitable for long-term use; and (4) safety considerations [26]. Similar to TU, testosterone gel, first introduced in 2000, is also a common treatment modality for LOH [27]. In the analysis of keyword burst, "testosterone gel" was one of the representative burst keywords as well. Clearly, these two representative burst keywords reflect the diversity of treatment modalities for LOH. Numerous studies have proven that TRT can improve immediate symptoms and minimize the long-term sequelae of testosterone deficiency itself [6, 26, 29, 30]. Regarding TRT for LOH patients, there are several areas of uncertainty that need to be further addressed in the future: (1) TRT and cardiovascular risk; (2) TRT and prostate health; and (3) TRT and metabolic syndrome [6, 31]. In addition to medical approach, a holistic approach is also an important treatment approach of LOH and recommended by most guidelines [6, 29].

4.3.2 Leydig cells

Testosterone is a cholesterol-derived steroid hormone, and is predominantly synthesized in the testicular Leydig cells [32–34]. With the aging process, the ability of Leydig cells to produce testosterone reduces, resulting in testosterone levels declining [34]. In the aged Leydig cells' steroidogenic pathway, a number of defects associated with reduced testosterone formation have been identified [34]. However, the exact mechanism of these age-related defects remains obscure. Accumulating evidences have demonstrated that changes in the oxidant/antioxidant balance within the Leydig cells are crucial to reduce the testosterone production ability [35]. In the LOH field, most research focused on clinical studies (86.9%), and there was only a small proportion of experimental studies (13.1%). In the analysis of keyword burst, "Leydig cells" was a representative burst keyword. Undoubtedly, the promotion of experimental studies, such as those involving Leydig cells, can improve the understanding of the mechanism and innovative treatments in LOH.

4.4 Limitations

The analysis in this study was based on the documents in the WoSCC database to retain all information in the literature and ensure the highest possible literature quality. The WoSCC database is the world's leading citation database, containing records from the highest-impact journals worldwide. However, we did not retrieve literature from other databases such as PubMed, Scopus, Embase, or the Cochrane Library. It may overlook significant clinical guidelines or studies published in local journals or in open-access literature in those databases. Second, bibliometric and scientometric analysis is a macroscopic method for LOH research hotspots, and can only be selected for a period of time, which can lead to more recent articles being cited less frequently than earlier articles.

5. Conclusions

This bibliometric and scientometric analysis provided a comprehensive overview of LOH studies from 2002 to 2024 and yielded quantitative and qualitative insights. The study identified the most prominent publications, journals, countries, institutions and authors in LOH research. The Keyword burst analysis demonstrates the latest research trends and hotspots ("TRT" and "Leydig cells"). Future studies should emphasize the establishment of an optimal and unified terminology, along with the promotion of experimental studies.

TABLE 4. Available oral and injectable testosterone undecanoate formulations.

Formulation/ Commercial name	FDA approval	T_{max}	$T_{1/2}$	Standard dosage	Pros	Cons
Oral Formulation						
Andriol[1]	No	4–5 h	4 h	120–240 mg 2–3 times daily	− Oral convenience − Reduction of liver involvement − Modifiable dosage − Quick reversal	− Unpredictable absorption depending on fat intake − Must be taken with fatty meals
Jatenzo[2]	Yes April 2019	5 h	2–5 h	158, 198, 237 mg 2 times daily	− Oral convenience − Reduction of liver involvement − Modifiable dosage − Quick reversal	− Must be taken with meals − Increase in blood pressure − Gastrointestinal side effects
Tlando[2]	Yes March 2022	4–6 h	2–5 h	112.5, 225 mg 1–2 times daily	− Oral convenience − Reduction of liver involvement − No titration − Quick reversal	− Must be taken with meals − Increase in blood pressure − Gastrointestinal side effects
Kyzatrex[2]	Yes August 2022	4–5 h	2–5 h	100, 150, 200 mg 2 times daily	− Oral convenience − Reduction of liver involvement − Modifiable dosage − Quick reversal	− Must be taken with meals − Increase in blood pressure − Gastrointestinal side effects
Injectable Formulation						
Aveed	Yes March 2014	4 d	34 d	750 mg (3 mL) IM; then 4 wk; then every 10 wk	− No titration − Long-lasting − Less frequent administration	− Pain at the injection site reaction (*e.g.*, pain) − Not allowing rapid drug withdrawal
Nebido	No	7 d	34 d	1000 mg (4 mL) IM every 10–14 wk	− No titration − Long-lasting − Less frequent administration	− Pain at the injection site reaction (*e.g.*, pain) − Not allowing rapid drug withdrawal

[1]*castor oil/propylene glycol vehicle;* [2]*self-emulsifying delivery system; IM: intramuscular injection; FDA: Food and Drug Administration;* T_{max}*: peak time;* $T_{1/2}$*: half life.*

ABBREVIATIONS

ADAM, androgen decline in the aging male; ADS/TDS, androgen/testosterone deficiency syndrome; AHCI, Arts & Humanities Citation Index; AOH, adult-onset hypogonadism; ASA, American Society of Andrology; CCR-EXPANDED, Current Chemical Reactions; CPCI-S, Conference Proceedings Citation Index-Science; CPCI-SSH, Conference Proceedings Citation Index-Social Science & Humanities; EAA, European Academy of Andrology; EAU, European Association of Urology; EMAS, European Male Aging Study; ESCI, Emerging Sources Citation Index; FDA, Food and Drug Administration; HI, high-income; HIV, human immunodeficiency virus; IC, Index Chemicus; IM, intramuscular injection; IPSS, International Prostate Symptom Score; ISA, International Society of Andrology; ISSAM, International Society for the Study of the Aging Male; ISSM, International Society for Sexual Medicine; LI, low-income; LMI, lower-middle income; LOH, late-onset hypogonadism; LUTS, lower urinary tract symptoms; PADAM, partial ADAM; PDE5i, phosphodiesterase-5 inhibitor; QoL, quality of life; SCI-EXPANDED, Science Citation Index Expanded; SMSNA, Sexual Medicine Society of North America; SSCI, Social Sciences Citation Index; $T_{1/2}$, half life; T_{max}, peak time; TRT, testosterone replacement therapy; TU, testosterone undecanoate; UMI, upper-middle income; WoSCC, Web of Science Core Collection.

AVAILABILITY OF DATA AND MATERIALS

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

AUTHOR CONTRIBUTIONS

PG—designed the study, performed the statistical analysis, wrote the manuscript and interpreted the data. HZ, WQL and XYW—participated in the conception and design of the study. JQW and NHS—participated in the conception and design of the study, and reviewed and edited the manuscript. All authors have read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

ACKNOWLEDGMENT

Not applicable.

FUNDING

This study was funded by the Training Programs of Innovation and Entrepreneurship for College Students in Jiangsu Province (202310313125Y), the Xuzhou Medical Leading Talents Training Project (XWRCHT20210027), the Innovation and Entrepreneurship Program of Xuzhou Medical University Science Park (CXCYHZZ2022002) and the 2024 Scientific Research Program of the Affiliated Hospital of Xuzhou Medical University (2024ZL08).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at https://oss.jomh.org/files/article/20718369256882012l6/attachment/Supplementary%20material.docx.

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How to cite this article: Peng Ge, He Zhang, Wenqing Liu, Xiaoyang Wang, Junqi Wang, Ninghong Song. Bibliometric and scientometric analysis of late-onset hypogonadism in the past two decades: knowledge mapping and research trends. Journal of Men's Health. 2026; 22(6): 64-76. doi: 10.22514/jomh.2026.052.