Review Article

Analysis of the Research Hotspot of Drug Treatment of Tuberculosis: A Bibliometric Based on the Top 50 Cited Literatures

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Objective. The objective of the current study was to analyze the research hotspot of drug treatment for tuberculosis via top literatures. Materials and Methods. A retrospective analysis was performed on June 7th, 2021. Literatures were searched on the Web of Science Core Collection to identify the top 50 cited literatures related to drug treatment of tuberculosis. The characteristics of the literatures were identified. The outcomes included authorship, journal, study type, year of publication, and institution. Cooccurrence network analysis and visualization were conducted using the VOS viewer (Version 1.6.16; Leiden University, Leiden, The Netherlands). Results. The top 50 cited literatures were cited 308 to 2689 times and were published between 1982 and 2014. The most studied drugs were the first-line drugs such as isoniazid and rifampicin (n = 22), and drug-resistant tuberculosis was most frequently reported (n = 16). They were published in 18 journals, and the New England Journal of Medicine published the most literatures (n = 18), followed by the American Journal of Respiratory and Critical Care Medicine (n = 7), and the Lancet (n = 6). The authors were from 13 countries, and the authors from the USA published most of the literatures (n = 30), while authors from other countries published less than five literatures. The CDC in the USA (n = 4), the World Health Organization (WHO) (n = 3), and the American Philosophical Society (n = 3) were the leading institutions, and only two authors published at least two top-cited literatures as first authors. Conclusions. This study provides insights into the development and most important literatures on drug therapy for tuberculosis and evidence for future research on tuberculosis treatment.

1. Introduction

Tuberculosis is the disease with the largest number of deaths caused by a single pathogen in the world. Based on the World Health Organization (WHO) global tuberculosis report, 10 million people were infected with tuberculosis and 1.5 million died in 2018 [1]. Tuberculosis is still the infectious disease that kills most people worldwide, resulting in a large disease burden [1–3]. Tuberculosis is caused by Mycobacterium tuberculosis, and it spreads through the air. It destroys the lungs and other systems and organs in the human body, and it forms tubercles, infiltration, caseation, or cavities, resulting in long-term low fever, expectoration, hemoptysis, and even death [4, 5].

Tuberculosis is preventable and treatable, and its main treatment is drug therapy (chemotherapy). There are over ten kinds of antituberculosis drugs in the world. The modern tuberculosis control strategy (directly observed treatment
| Title                                                                 | Journal                                      | Article type | Research contents/drugs                                                                 | Total citation | Publication year | Page number | PMID          |
|----------------------------------------------------------------------|----------------------------------------------|--------------|----------------------------------------------------------------------------------------|----------------|------------------|-------------|---------------|
| Tuberculosis associated with infliximab, a tumor necrosis factor (alpha)-neutralizing agent [27] | *New England Journal of Medicine*            | Article      | Infliximab                                                                            | 2689           | 2001             | 6           | 11596589      |
| American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: treatment of tuberculosis [28] | *American Journal of Respiratory and Critical Care Medicine* | Review       | Therapeutic monitoring                                                                 | 1380           | 2003             | 59          | 12588714      |
| The emergence of drug-resistant tuberculosis in New York City [29]    | *New England Journal of Medicine*            | Article      | Drug-resistant, rifampentine, isoniazid, HIV coinfection                              | 786            | 1993             | 5           | 8381207       |
| A small-molecule nitroimidazopyran drug candidate for the treatment of tuberculosis [30] | *Nature*                                    | Article      | Nitroimidazopyran                                                                     | 772            | 2000             | 4           | 10879539      |
| The challenge of new drug discovery for tuberculosis [31]             | *Nature*                                    | Review       | New drugs                                                                            | 757            | 2011             | 7           | 21270886      |
| Multidrug-resistant and extensively drug-resistant tuberculosis: a threat to global control of tuberculosis [32] | *Lancet*                                    | Article      | Drug resistance                                                                       | 716            | 2010             | 13          | 20488523      |
| Global surveillance for antituberculosis-drug resistance, 1994-1997 [33] | *New England Journal of Medicine*            | Article      | Drug resistance, isoniazid, rifampin, pyrazinamide, ethambutol                        | 706            | 1998             | 8           | 9614254       |
| An official ATS statement: hepatotoxicity of antituberculosis therapy [34] | *American Journal of Respiratory and Critical Care Medicine* | Review       | Hepatotoxicity                                                                       | 675            | 2006             | 17          | 17021358      |
| Treatment of 171 patients with pulmonary tuberculosis resistant to isoniazid and rifampin [35] | *New England Journal of Medicine*            | Article      | Drug resistance                                                                       | 627            | 1993             | 5           | 8426619       |
| The diarylquinoline TMC207 for multidrug-resistant tuberculosis [10]  | *New England Journal of Medicine*            | Article      | TMC207, drug-resistant                                                                | 590            | 2009             | 8           | 19494215      |
| Anti-tumour necrosis factor agents and tuberculosis risk: mechanisms of action and clinical management [36] | *Lancet Infectious Diseases*                 | Review       | Infliximab, etanercept                                                                | 571            | 2003             | 7           | 12614731      |
| Advances in the development of new tuberculosis drugs and treatment regimens [37] | *Nature Reviews Drug Discovery*              | Review       | New drug regimen                                                                     | 567            | 2013             | 16          | 23629506      |
| Drug-therapy - treatment of multidrug-resistant tuberculosis [38]      | *New England Journal of Medicine*            | Review       | Drug resistance                                                                       | 555            | 1993             | 7           | 8350889       |
| Incidence of serious side effects from first-line antituberculosis drugs among patients treated for active tuberculosis [39] | *American Journal of Respiratory and Critical Care Medicine* | Review       | Adverse reactions, isoniazid, rifampin, pyrazinamide, ethambutol                     | 526            | 2003             | 5           | 12569078      |
| Three months of rifapentine and isoniazid for latent tuberculosis infection [40] | *New England Journal of Medicine*            | Article      | Latent tuberculosis, rifapentine, isoniazid                                          | 514            | 2011             | 11          | 22150035      |
| Title                                                                 | Journal                                      | Article type | Research contents/drugs                                      | Total citation | Publication year | Page number | PMID         |
|----------------------------------------------------------------------|----------------------------------------------|--------------|--------------------------------------------------------------|----------------|------------------|-------------|--------------|
| The effect of directly observed therapy on the rates of drug-        | New England Journal of Medicine              | Article      | Directly observed treatment, drug resistance                 | 496            | 1994             | 5           | 8139628     |
| resistance and relapse in tuberculosis [41]                        |                                              |              |                                                              |                |                  |             |              |
| Delamanid for multidrug-resistant pulmonary tuberculosis [11]        | New England Journal of Medicine              | Article      | Delamanid (OPC-67683), drug-resistant                       | 488            | 2012             | 9           | 22670901    |
| Efficacy of various durations of isoniaizid preventive therapy for   | Bulletin of The World Health Organization   | Article      | Isoniazid                                                   | 484            | 1982             | 9           | 6754120     |
| tuberculosis - 5 years of follow-up in the IUAT trial [42]          |                                              |              |                                                              |                |                  |             |              |
| Effectiveness of recommendations to prevent reactivation of latent  | Arthritis and Rheumatism                     | Article      | Inflliximab, latent tuberculosis                             | 484            | 2005             | 6           | 15934089    |
| tuberculosis infection in patients treated with tumor necrosis factor|                                              |              |                                                              |                |                  |             |              |
| antagonists [43]                                                    |                                              |              |                                                              |                |                  |             |              |
| Timing of initiation of antiretroviral drugs during tuberculosis     | New England Journal of Medicine              | Article, trail| Antiretroviral therapy, HIV coinfection                     | 483            | 2010             | 9           | 20181971    |
| therapy [44]                                                       |                                              |              |                                                              |                |                  |             |              |
| Literatures on the treatment of tuberculosis undertaken by the       | International Journal of Tuberculosis and   | Review       | Isoniazid, rifampicin, pyrazinamide, ethambutol, streptomycin| 476            | 1999             | 48          | 10529902    |
| British Medical Research Council Tuberculosis Units, 1946-1986, with|||                                                              |                |                  |             |              |              |
| relevant subsequent publications [45]                               |                                              |              |                                                              |                |                  |             |              |
| Standard short-course chemotherapy for drug-resistant tuberculosis  | JAMA-Journal of the American Medical         | Article      | Drug-resistant, isoniaizid, rifampicin, pyrazinamide,        | 465            | 2000             | 8           | 10815117    |
| - treatment outcomes in 6 countries [46]                            | Association                                  |              | ethambutol, streptomycin                                     |                |                  |             |              |
| Treatment of tuberculosis in patients with advanced human-          | New England Journal of Medicine              | Article      | HIV coinfection, isoniaizid, rifampin, pyrazinamide,         | 451            | 1991             | 5           | 1898769     |
| immunodeficiency-virus infection [47]                               |                                              |              | ethambutol                                                   |                |                  |             |              |
| Antituberculosis drugs: ten years of research [48]                  | Bioorganic & Medicinal Chemistry             | Review       | New drugs                                                   | 439            | 2007             | 34          | 17291770    |
| Short, highly effective, and inexpensive standardized treatment of  | American Journal of Respiratory and Critical| Article      | Drug-resistant, gatifloxacin, clofazimine, ethambutol,       | 436            | 2010             | 8           | 20442432    |
| multidrug-resistant tuberculosis [49]                               | Care Medicine                                |              | pyrazinamide, prothionamide, kanamycin, isoniazid            |                |                  |             |              |
| High-dose vitamin D-3 during intensive-phase antimicrobial treatment | Lancet                                       | Article      | Vitamin D, supplementary                                     | 427            | 2011             | 8           | 21215445    |
| of pulmonary tuberculosis: a double-blind randomised controlled trial|                                              |              |                                                              |                |                  |             |              |
| Supplement – American Thoracic Society Centers for Disease Control  | American Journal of Respiratory and Critical| Review       | Latent tuberculosis infection, rifampin                      | 415            | 2000             | 27          | 10764341    |
| and Prevention – targeted tuberculin testing and treatment of latent | Care Medicine                                |              |                                                              |                |                  |             |              |
| tuberculosis infection [51]                                         |                                              |              |                                                              |                |                  |             |              |
| Antituberculosis drug-induced hepatotoxicity: concise up-to-date     | Journal of Gastroenterology and Hepatology   | Review       | Hepatotoxicity, first-line drugs                             | 410            | 2008             | 11          | 17995946    |
| review [52]                                                         |                                              |              |                                                              |                |                  |             |              |
| Title                                                                 | Journal                                      | Article type | Research contents/drugs                                                                 | Total citation | Publication year | Page number | PMID         |
|----------------------------------------------------------------------|----------------------------------------------|--------------|----------------------------------------------------------------------------------------|---------------|-----------------|-------------|--------------|
| Chemotherapy and management of tuberculosis in the United Kingdom: recommendations 1998 [53] | Thorax                                       | Review       | Guidelines on chemotherapy                                                               | 409           | 1998            | 12          | 9797751     |
| Multidrug resistant pulmonary tuberculosis treatment regimens and patient outcomes: an individual patient data meta-analysis of 9,153 patients [54] | Plos Medicine                                | Review       | Drug-resistant, fluoroquinolones, ethionamide, prothionamide                            | 407           | 2012            | 0           | 22952439    |
| Treatment outcomes among patients with multidrug-resistant tuberculosis: systematic review and meta-analysis [55] | Lancet Infectious Diseases                   | Review       | Drug-resistant, treatment regimens                                                      | 406           | 2009            | 8           | 19246019    |
| WHO guidelines for the programmatic management of drug-resistant tuberculosis: 2011 update [56] | European Respiratory Journal                 | Article      | Guidelines, drug-resistant                                                               | 405           | 2011            | 12          | 21828024    |
| Timing of antiretroviral therapy for HIV-1 infection and tuberculosis [57] | New England Journal of Medicine              | Article      | Antiretroviral therapy, HIV coinfection                                                 | 403           | 2011            | 9           | 22010914    |
| The potential advantages of nanoparticle drug delivery systems in chemotherapy of tuberculosis [58] | American Journal of Respiratory and Critical Care Medicine | Article | Nanoparticle-based drug delivery systems                                                | 403           | 2005            | 4           | 16151040    |
| Effect of isoniazid prophylaxis on incidence of active tuberculosis and progression of HIV-infection [59] | Lancet                                       | Article      | Isoniazid, HIV coinfection                                                               | 397           | 1993            | 4           | 8101302     |
| Community-based therapy for multidrug-resistant tuberculosis in Lima, Peru [60] | New England Journal of Medicine              | Article      | Drug-resistant, pyrazinamide, ethambutol                                                | 392           | 2003            | 9           | 12519922    |
| Multidrug-resistant tuberculosis and culture conversion with bedaquiline [61] | New England Journal of Medicine              | Article      | Bedaquiline (Sirturo, TMC207), drug-resistant                                            | 387           | 2014            | 10          | 25140958    |
| Best drug treatment for multidrug-resistant and extensively drug-resistant tuberculosis [62] | Lancet Infectious Diseases                   | Article      | Drug-resistant, multiple drugs                                                           | 379           | 2010            | 9           | 20797644    |
| Linezolid for treatment of chronic extensively drug-resistant tuberculosis [63] | New England Journal of Medicine              | Article      | Linezolid, drug-resistant                                                               | 365           | 2012            | 11          | 23075177    |
| Integration of antiretroviral therapy with tuberculosis treatment [64] | New England Journal of Medicine              | Article      | Integrating antiretroviral therapy, HIV coinfection                                      | 358           | 2011            | 10          | 22010915    |
| Efficacy of trimethoprim-sulphamethoxazole prophylaxis to decrease morbidity and mortality in HIV-1-infected patients with tuberculosis in Abidjan, Cote d’Ivoire: a randomised controlled trial [65] | Lancet                                       | Article      | Trimethoprim-sulphamethoxazole, HIV coinfection                                        | 355           | 1999            | 7           | 10232312    |
| Four-month moxifloxacin-based regimens for drug-sensitive tuberculosis [66] | New England Journal of Medicine              | Article      | Moxifloxacin, isoniazid, rifampin, pyrazinamide, ethambutol                             | 355           | 2014            | 11          | 25196020    |
| Toxic hepatitis with isoniazid and rifampin – a meta-analysis [67] | Chest                                        | Review       | Hepatotoxicity, isoniazid, rifampin                                                     | 344           | 1991            | 7           | 1824929     |
short-course, DOTS) based on short-term chemotherapy was proposed by the WHO. This strategy recommends 4-6 standard antibiotics for 6-8 months of treatment for active and drug-sensitive tuberculosis, and this is still an important way to treat and control tuberculosis [6]. The common first-line oral antituberculosis drugs include isoniazid, rifampin, pyrazinamide, and ethambutol [7]. For multidrug-resistant tuberculosis with reduced sensitivity to first-line antituberculosis, second-line drugs (such as p-amino salicylic acid, ethylisonicotinic acid, cycloserine, and tertizide), injectable antituberculosis drugs (such as streptomycin, kanamycin, amikacin, and capreomycin), and quinolones (such as levofloxacin, moxifloxacin, and gatifloxacin) can be used. For the treatment of extensively drug-resistant tuberculosis, new antituberculosis drugs can also be used, such as the new mechanism and new target antituberculosis drugs that are represented by betaquiline and delamanine, which were recently introduced onto the market [8-12].

Bibliometrics is a cross-science that uses mathematical and statistical methods to quantitatively analyze all knowledge carriers [13]. It has been widely used for quantitative research assessment exercises of academic output [14, 15]. Citation analysis is the main bibliometric method [16], and the number of citations reflects the impact of an article in the scientific community to a certain extent. Highly cited literatures are considered to be the basis of research fields [17, 18]. Therefore, the analysis of highly cited articles can provide information on the scientific progress and research trends within a specific discipline [19]. Currently, many literatures related to citation analysis have been published in areas such as diabetes [20], surgery [21], anesthesia [22], rehabilitation [23], and vaccines [24], and there are some highly cited tuberculosis-related literatures [25, 26]; however, no study on tuberculosis chemotherapy has been published and the research hotspot is still unclear. Thus, we performed the current study to analyze the research hotspot of drug treatment of tuberculosis by analyzing the top literatures.

2. Materials and Methods

We performed a study to analyze the published literature on drug treatment of tuberculosis. This study did not involve human patients, and therefore, it did not require institutional review board approval.

2.1. Search Strategy. We performed a search for literatures on drug treatment of tuberculosis in the Web of Science Core Collection on June 7th, 2021. The search terms were “TS= (TB OR tuberculosis OR tuberculoses OR Kochs)"
The search results were sorted by citation, and articles that had more citations were ranked higher.

2.2. Article Selection. Two authors independently screened the abstracts and full texts to identify the top 50 cited literatures on drug treatment of tuberculosis. Only articles that focused on the subject of drug treatment of tuberculosis were included. A drug treatment of tuberculosis article was defined as any study that focused on drug treatment of tuberculosis. Articles about in vitro research, animal experiments, or drug mechanism research were excluded. In addition, literatures that only mentioned drug treatment of tuberculosis but not its main research purpose were also excluded. Disagreements were resolved by discussion.

2.3. Data Extraction. Two authors independently extracted data from the top 50 cited literatures. The data that were extracted included the title, abstract, source journal, publication time, article types, number of authors, name of the first author and corresponding author, author affiliation, country, and journal impact factor.
2.4. Data Analysis. After summarizing the relevant content, as mentioned above, all of the data were analyzed by using SPSS software [9]. The data were analyzed using the VOS viewer software to show the journals, countries, institutions, authors, and keywords in the research field of tuberculosis drug therapy.

3. Results

The top 50 cited literatures are presented in Table 1. The top 50 cited literatures were identified based on their citations. Overall, there were 26,499 citations, with a range of 308 to 2689 citations, while the average was 530 citations and the median was 432 citations. The most frequently mentioned drugs were the first-line drugs \((n = 22)\), which were represented by isoniazid and rifampicin, followed by new drugs \((n = 16)\). There were 16 literatures related to drug-resistant tuberculosis, nine literatures related to HIV coinfection, seven literatures related to drug therapeutic schedules, six literatures related to adverse drug reactions (mainly about hepatotoxicity), and two literatures related to supportive drugs.

These literatures were published in 18 journals (Table 2). Most were published in the New England Journal of Medicine \((n = 18)\), followed by the American Journal of Respiratory and Critical Care Medicine \((n = 7)\), Lancet \((n = 6)\), Lancet Infectious Diseases \((n = 3)\), Nature \((n = 2)\), and JAMA \((n = 2)\). Only one article was published in each of the other 12 journals. The journals’ impact factors ranged from 2.268 to 74.699. Figure 1 shows the collaborative networks of journals that published the top 50 cited literatures. The size of each circle was determined by citations. Additionally, the line in the visualization indicates the relatedness of the journals in terms of cocitation links.

All literatures were published over 33 years, from 1982 to 2014 (Table 3). The highest number of literatures was published in 2003 \((n = 4)\), and the maximum contribution of publications was made within a 5-year period from 2010 to 2014 \((n = 16)\).

All literatures were from 13 countries (Table 4). The number of literatures (based on correspondence) from the United States \((n = 30)\) accounts for 60% of the total. We obtained the same results by analyzing the source countries.
of all authors (Table 5). The number of literatures by authors from other countries, including Switzerland, England, Belgium, Canada, South Africa, Spain, China, Denmark, France, the Netherlands, Scotland, and Cote d’Ivoire, was less than five. The difference is that more corresponding authors are from Belgium and more participating authors are from South Africa. From VOS viewer analysis in Figure 2, each node represented a country and lines between the nodes indicated the strength of the relation between countries. The lines’ strength of the USA showed a strong connection with others and a great impact on other countries’ research.

Among the 50 literatures, all the authors belong to 195 institutions in total. Five institutions (based on the corresponding author) contributed more than two literatures (Table 6). The five institutions were from three countries, including the USA (n = 3), Switzerland (n = 1), and South Africa (n = 1). The top three contributors were CDC in the USA (n = 4), the WHO (n = 3), and the American Philosophical Society (n = 3). As can be seen from Table 7 and Figure 3, a total of 23 institutions met the threshold of a minimum of 2 publications of the 50 top-cited literatures. It includes 12 American institutions, 3 Korean institutions, 2 South African institutions, 2 British institutions, and Switzerland, Canada, and the Philippines each have one institution. In Figure 3, each node represents an institution; the links represent the association between institutions; and the color and distance between items represent the similarity between institutions. As shown in the network, the Centers for Disease Control and Prevention and WHO linked the most, which meant they had the strongest collaborations with other institutions. Comparing the institutions of the corresponding authors who published more articles with the institutions of all authors, it can be seen that most are Centers for Disease Control and Prevention and the World Health Organization. In addition to the top two institutions,

Table 6: Institutions that published at least two of the corresponding author of 50 top-cited literatures.

| Institution                              | Country     | Number of study |
|------------------------------------------|-------------|---------------|
| Centers for Disease Control and Prevention | USA         | 4             |
| WHO (World Health Organization)         | Switzerland | 3             |
| ATS (American Thoracic Society)         | USA         | 3             |
| University of KwaZulu-Natal             | South Africa| 2             |
| National Jewish Health Center           | USA         | 2             |
there are some differences between the following institutions, and the participating authors are mostly from different universities.

Among the 50 literatures, there were only two first authors who contributed more than two literatures as the first author. They were Diacon, Andreas H from the
University of Stellenbosch in South Africa and Karim, Salim S. Abdool from the University of KwaZulu-Natal in South Africa. No corresponding author published more than one study (Table 8). Table 9 shows all the authors involved in two or more studies. Among them, Andres, Koen., Iseman, MD., Lounis, and Nacer participated in three studies. These authors are mainly from South Africa (n = 9), the United States (n = 6), Belgium (n = 4), Switzerland, Australia, South Korea, and the United Kingdom (n = 1). KwaZulu Natal Union (n = 4), Janssen (Pharmaceutical Companies of Johnson & Johnson, n = 4), and the Centre for the AIDS Program of Research in South Africa (CAPRISA, n = 3) were the most frequent institutions of these authors.

Table 8: Authors who published at least two literatures as first authors or corresponding authors.

| Author       | Name                      | Number of study | Institution                                      | Country      |
|--------------|----------------------------|-----------------|--------------------------------------------------|--------------|
| First author | Diacon, Andreas H.        | 2               | University of Stellenbosch                       | South Africa |
|              | Karim, Salim S. Abdool    | 2               | University of KwaZulu-Natal                      | South Africa |

Table 9: Authors of the top 50 cited literatures.

| Name                  | Weight of documents | Institution                                                                 | Country        |
|-----------------------|--------------------|-----------------------------------------------------------------------------|----------------|
| Andries, Koen         | 3                  | Janssen Research and Development                                           | Belgium        |
| Iseman, MD            | 3                  | National Jewish Center for Immunology and Respiratory Medicine              | USA            |
| Lounis, Nacer         | 3                  | Tibotec BVBA, Johnson & Johnson                                             | Belgium        |
| Baxter, Cheryl        | 2                  | The Centre for the AIDS Program of Research in South Africa (CAPRISA)      | South Africa   |
| De Marez, Tine        | 2                  | Janssen Research and Development                                           | USA            |
| Diacon, Andreas H.    | 2                  | University of Stellenbosch                                                 | South Africa   |
| Dye, C                | 2                  | World Health Organization (WHO)                                            | Switzerland    |
| Friedland, Gerald     | 2                  | Yale University                                                            | USA            |
| Gandhi, Neel R.       | 2                  | Albert Einstein College of Medicine                                         | USA            |
| Gengiah, Tanuja       | 2                  | The Centre for the AIDS Program of Research in South Africa (CAPRISA)      | South Africa   |
| Grobler, Anneke       | 2                  | University of Melbourne                                                    | Belgium        |
| Horsburgh, Cr         | 2                  | Boston University                                                          | USA            |
| Karim, Quarraisha     | 2                  | University of KwaZulu-Natal                                                 | South Africa   |
| Abdool                | 2                  | University of KwaZulu-Natal                                                 | South Africa   |
| Karim, Salim S. Abdool| 2                  | University of KwaZulu-Natal                                                 | South Africa   |
| Kim, Sj               | 2                  | Seoul Natl University                                                      | Korea          |
| Meyvisch, Paul        | 2                  | Galapagos NV                                                               | Belgium        |
| Naidoo, Kogieleum     | 2                  | University of KwaZulu-Natal                                                 | South Africa   |
| Nair, Gonasagrie      | 2                  | The Centre for the AIDS Program of Research in South Africa (CAPRISA)      | South Africa   |
| Padayatchi, Nesri     | 2                  | University of KwaZulu-Natal                                                 | South Africa   |
| Pym, Alexander        | 2                  | KwaZulu-Natal Research Institute for TB & HIV                              | South Africa   |
| Raviglione, Mc        | 2                  | University of Milan                                                        | Italy          |
| Sterling, Timothy R.  | 2                  | Vanderbilt University                                                      | USA            |
| Van Heeswijk, Rolf P. G.| 2                   | Janssen Infectious Diseases BVBA                                            | Belgium        |
| Zumla, Alimuuddin     | 2                  | University College London                                                  | England        |
published articles are roughly divided into four relatively independent groups, while there is a complex correlation between other authors.

From the retrieved publications, keywords were extracted and cooccurrence frequencies were calculated. In total, 243 keywords were extracted and the network of keyword cooccurrence is shown in Figure 6. The size of the circles indicates the total frequency of occurrence for the keywords in the top 50 cited literatures. From the density map displayed in Figure 7, colors range from blue to green to yellow. The yellow area represents the research hotspots and directions in this field. The keywords mostly focused on pulmonary tuberculosis, etiology, drug resistance, tuberculosis complicated with HIV, treatment scheme selection, cost effectiveness and efficacy, epidemiology and transmission, and preventive therapy. Pulmonary tuberculosis, drug resistance, and treatment strategies turned out to be important topics.

4. Discussion

Among the diseases that are caused by a single pathogen, the disease burden of tuberculosis has been the highest for many years worldwide. Although the effectiveness of drug treatment for tuberculosis has been known for a long time, because of an increasing population flow, an increase in the human immunodeficiency virus (HIV) infection rate, irregular chemotherapy, treatment interruption, and other factors leading to the emergence of drug-resistant strains [75], tuberculosis is still prevalent throughout the world and cannot be eliminated in the short-term. Research has shown that among newly diagnosed patients, approximately 5% are drug-resistant tuberculosis patients [76]. The probability of coinfecion with tuberculosis in patients with immune deficiency diseases within 10 years was 8%, and the mortality rate of these patients with a coinfection was as high as 30%, which was higher than the mortality rate of tuberculosis patients in the general population [77]. Therefore, the prevention and treatment of tuberculosis is still a great challenge. Drug treatment is still the main means to treat tuberculosis, and it would likely be the main treatment at present, even in the future for a long time [78]. Previously, bibliometric analysis literatures on tuberculosis [25, 26] did not focus on drug treatment, so we performed a study to evaluate research hotspots on tuberculosis drug therapy via top literatures.

The 50 top-cited literatures were published in 18 different journals between 1982 and 2014. The New England Journal of Medicine was the most frequent journal on our list, with 18 literatures (36%), followed by the American Journal
of Respiratory and Critical Care Medicine, Lancet, Lancet Infectious Diseases, Nature, and JAMA.

This study found that the top-cited literatures were from many different countries, institutions, and authors. However, the USA showed a powerful influence, with approximately 60% of the literatures originating from institutions in the USA. Three of the five institutions that contributed more than two literatures were from the USA, among which the CDC and the American Psychological Society had a high influence in the field of tuberculosis treatment. The USA showed a strong connection with others and a great impact on other countries' research. In addition, the number of literatures from the WHO ranked highly, indicating that tuberculosis was a disease of global concern and that the WHO attached great importance to it. To understand the differences between the countries and institutions to which the corresponding authors and participating authors belong, we compared them. We found that there was no significant change in the results, but more participating authors came from different universities. The reason may be that most of the participating authors are school students.

The authors of the top-cited literatures on drug treatment of tuberculosis were located throughout the world. There were only two authors who contributed more than two literatures as first author. No corresponding author published more than one study. Possible reasons for this might include the following: first, tuberculosis had a wide range of influence, there were many institutions and researchers studying the disease, and these institutions and researchers were widely distributed; second, first-line oral antituberculosis drugs, including isoniazid, rifampicin, pyrazinamide, and ethambutol, had been commonly used internationally in the treatment of tuberculosis for many years [2], which lowered the threshold of research; and third, there were many kinds
of drugs that could be used to treat tuberculosis, and they had different mechanisms, targets, and strategies [78], leading to more scattered cut-in points in research. Through the analysis of authors at different levels, it was found that the coauthors with more published articles are roughly divided into four relatively independent groups, while there is a complex correlation between other authors. In addition, South African authors have made greater contributions, which may be due to the high prevalence of tuberculosis in South Africa, which is an important research topic for their local health institutions.

Important achievements have been made in research on new antituberculous drugs. In the last 50 years, the first new-mechanism antituberculous drug, beta-lutamine, and the former nitroimidazole drug, delamanide, were approved for marketing. A variety of new mechanisms and new targets of antituberculosis candidates have entered the clinical stage [78]. For example, the nitroimidazole drug PA-824 [10] was in phase III clinical trials, and its mechanism of action involved inhibiting the synthesis of mycobacterial proteins and mycolic acid. The ethambutol drug SQ-109 was in phase II clinical trial, and its mechanism of action was inhibition of mycobacterium cell wall synthesis [79]. Combined with the visualization results, new drug treatments for drug-resistant tuberculosis and coinfection might be hot spots in future top-cited articles.

Our study also had some limitations. First, the citation analysis was based on the Web of Science Core Collection, which might miss some important literatures that were indexed by other databases, resulting in biased results. Second, searching using a topic search meant that a small number of manuscripts that involved drug treatment of tuberculosis might not have been identified. Third, this study excluded literatures that mentioned drug treatment of tuberculosis but that did not include tuberculosis as its main purpose of research, which were mainly reviews. Thus, it was possible that literatures with less content but a significant impact were missed. Fourth, since bibliometrics
includes secondary research (such as review), the keywords and research focus of the secondary research may be different from the original research, which may lead to bias. Fifth, leading organizations that issue guidelines about TB treatment such as the CDC, Atlanta in the USA, and the WHO, Geneva in Switzerland, also add to the geographical bias. Sixth, VOS viewer software was used for visual analysis in this article. The definition of weight may be different from the actual frequency. At the same time, due to its limitations, it is unable to analyze more complex correlations.

In conclusion, our study identified the research hotspot of drug treatment of tuberculosis. Tuberculosis has a great burden of disease worldwide. Drug treatment of tuberculosis has been an important research field, and it will continue to be important now and in the near future. With the increasing incidence of drug-resistant tuberculosis, coinfection, and the emergence of new drugs, there will be increasing-impact drug treatment for tuberculosis-related research in the future.

**Data Availability**

The data used to support the findings of this study are included in the article. The original data can be retrieved on the Web of Science.

**Ethical Approval**

This is a bibliometric analysis, so ethics approval is not applicable.

**Conflicts of Interest**

The authors declare that they have no conflicts of interest.

**Authors’ Contributions**

Yonggang Zhang designed the study; Ying Xiong analyzed the data and drafted the manuscript; Jinwen Wei, Yujia
Cai, Yang Zhang, and Li Feng drafted the manuscript. All authors approved the final version of the manuscript.

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