

Potential Diagnostic Markers of Mycobacterium Tuberculosis Infection: A Bibliometric Study (2019-2023)

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Abstract: Background: Chemokines initiate both innate and adaptive immune response, in spite of their chemotactic effects. Several investigations on animals have outlined the beneficial and harmful effects of chemokine ligands and their receptors on the organisms during tuberculosis (TB).

Aims:.....

Methods: This bibliometric analysis was conducted using the Scopus database. Many analysis, including those for the most prosperous nations, journals, authors, institutions, and articles, were performed on the papers that were retrieved. The existing condition, new areas of interest, and potential for chemokine and tuberculosis research were ascertained using co-occurrence mapping of phrases and keywords. VOSviewer and Bibliometrix were utilized to visualize the collaborative network mapping and evaluate the data. The results: The most common keywords were “chemokine” and “tubercukosis”. The Scopus search engine identified 802 Tuberculosis-related documents published by Global Countries between 2019 to 2023. According to our findings, United States was the most productive in Global Countries. In the early stages of the study, researchers investigated immune regulatory and signalling pathway in tuberculosis-related study. In recent years, the development of antivirus agents has emerged as a prominent topic. Conclusions: The study performed a bibliometric analysis of over 5 years of chemokine and tuberculosis research, identifying the nations, institution journal and publications active in this subject. The findings provide a comprehensive overview of chemokine in tuberculosis research.

The abstract consists of 150-200 words written in a single paragraph. It should be clear, informative, descriptive, and provide a clear statement of the problem, the proposed approach or solution, and point out major findings and conclusions. The abstract should be written in the past tense. Standard nomenclature should be used and abbreviations should be avoided. No literature should be cited. The abstract should be accompanied by relevant keywords or brief phrases related to the paper, with a maximum of 5 keywords.

Key words: Tuberculosis, Bibliometric analysis, chemokine.

1. Introduction

Tuberculosis (TB) is one of the ten causes of death and the main cause of infectious agents. About 1.3 million fatalities among HIV-negative individuals and approximately 300,000 deaths among HIV-positive individuals are attributable to tuberculosis. The 2023 World Health Organization (WHO) report gives a thorough and current evaluation of tuberculosis (TB) and the advancements made in the diagnosis, treatment, and prevention of this illness at the national, international, and local levels. This is

done within the framework of TB targets, plans, and commitments (1). The report's 2023 edition is based on information gathered by WHO from national health ministries as part of its yearly data collection. More than 99% of the world's population lives in 192 nations and territories, and statistics on tuberculosis cases is reported for 2023 (2).

The bacterium *Mycobacterium tuberculosis* is the main cause of the infectious disease tuberculosis (MTB) which can attack various organs in the body except nails, hair or feathers and most often attacks the lungs because the initial entry of the bacteria is inhalation. This disease, if not treated properly, can cause various complications and even death (3). Despite scientific advances in The detection and management of tuberculosis continues to be the biggest hazard to public health, particularly in developing nations. It is estimated that latent tuberculosis infection, in which an intracellular bacterium infects an individual without causing an active disease but still puts them at risk of becoming active again, affects one-third of the world's population. Approximately 10% of people with primary MTB infections have the potential to become active. Most of the other MTB are found in the lungs in structures known as granulomas, where they are latent (4).

Currently, latent tuberculosis infection (ITBL) can be detected using the interferon-gamma release assay (IGRA). This examination can only determine whether an individual has been exposed to TB germs called other tuberculosis, but does not help differentiate TBL infection from active TB disease. The principle of IGRA is to detect Interferon-gamma (IFN- γ) which is excreted by T cells as a response to stimulation of specific Mtb antigens. A cohort study with a large sample size in a country with a high TB infection rate comparing the effectiveness of IGRA and the tuberculin test showed that no significant differences were found. To diagnose latent tuberculosis infection, tuberculin test, and QFT-GIT. This is supported by other cohort studies with the same results, there is no significant difference in predicting adult TB infection in South Africa. IGRA sensitivity detects 75% positive TB and tuberculin test 76.9%, the effectiveness of both is less than 50%: IGRA 49.3% and tuberculin test 45.0%. This is a consideration in assessing the effectiveness of the IGRA test compared to the relatively cheaper tuberculin test (4).

Recent research as an alternative for TB diagnosis has identified a chemokine, namely interferon-gamma inducible protein 10 (IP10) (5). IP10 is a chemokine, namely interferon, which is excreted by cells that present antigens in response to IFN- γ by interacting with the CXCR3 receptor to control T cell migration to inflammatory areas. IP10 was found to increase in day 1 plasma that was not stimulated by adults and children suffering from TB (5). In HIV-infected patients the IP10 response is known to be greater and stronger than IFN- γ (6). IP10 can also be detected in patients with active TB and its levels decrease after receiving therapy (7). Patients with systemic symptoms, such as fever and anorexia, had higher levels of IP10 (8). The results of research on IP10 in patients infected with TB, both adults and children, were higher than controls, thus showing potential value for diagnosing latent TB (9). Sodium electrolyte examination is one of the examinations that plays an important role in TB patients which indicates an electrolyte imbalance between those receiving TB treatment (5). Examination of the neutrophil lymphocyte ratio (NLR) percentage value can play a role as an immune response in TB sufferers, because the neutrophil response will increase after 8-15 days of being infected with Mtb and then last until the end of the infection. These results provide an understanding of how important neutrophils are in the early phase of infection. The adaptive immune system against Mtb mainly relies on CD4+ cells, the role of CD4 which produces the cytokine interferon gamma (IFN- γ) in the incidence of primary resistance to Tuberculosis (TBC) has been successfully identified (10). Thoracic x-ray examination is very important for diagnosing TB patients. The x-ray results can show infiltrative spots or nodules, especially in the upper lobes. Apart from that, thoracic x-rays can also show the formation of cavities, calcified nodules such as tubercleoma and many small nodular lesions indicating Miler Tuberculosis (TBC). Radiological examination is very important for the diagnosis of Tuberculosis (TB). The presence of suggestive clinical symptoms of Tuberculosis (TB) is almost always an abnormality found on X-rays.

If clinically supportive but X-ray radiological examination >10 weeks post-infection is negative, then this is a strong sign that what is being suffered is not tuberculosis (11). Diagnosis currently still experiences many obstacles, especially collecting sputum specimens which do not comply with standards, especially in collecting sputum from elderly patients and children so that the results obtained are not optimal.

Analyzing the general trend of research activity and examining the relationships between pertinent research institutions can be done effectively with bibliometric studies. The bibliometric studies can assess the volume and trends of scientific output in important biomedical fields across nations and years. They are especially helpful for new fields whose effects on the broader field of biomedical research are still being completely assessed (32). We present this study on the scientific productions in this subject among countries over the last five years to better understand chemokine's boundaries and hot regions in tuberculosis research (2019-2023).

2. Research Methods

This research design is identification of research journal within 5 years, namely from 2019 to 2023. The research journal are those contain tuberculosis in Global Countries.

1.1 Sources of information and techniques for searching

For this study, all of the data were obtained from the Web of Scopus. To prevent variations, literature retrieval was done all in one day on January 1st, 2024, taking into account the speed at which databases are updated. This study was published over a four-decade span. The following were the search phrases used: TS stands for [interleukine OR tuberculosis]. Only original articles and reviews published in English were included among the several publication types.

2.2 Data collecting and cleaning

Comprehensive publishing parameters, such as the quantity of papers and citations, the H-index, the publication year, the nation or area, the affiliations, the authors, the journal, the references, and the keywords, were collected from the database for the current study. Spelling mistakes and duplicate writers were then eliminated. We believe that the majority of the original data are reliable, even though errors in the analysis may not be entirely prevented due to variations in the formats of referenced journals, different versions of cited references, and the same abbreviated name for several authors. Prior to data analysis using VOSviewer v.1.6.10.0 (Science and Technology Research Center, Leiden University, Leiden, the Netherlands), spelling mistakes were fixed, superfluous words were eliminated, and some repetitive terms were combined into one word. Lastly, for bibliometric analysis, cleaned data were imported into VOSviewer and the Bibliometrix software.

2.3 Bibliometric analysis

The two primary criteria for assessing the caliber of research are productivity, which is generally assessed by the number of publications, and impact, which is measured by the number of citations, with the exception of self-citation. The Hindex has gained popularity recently as a tool for assessing academic contributions made by scholars and forecasting their future scientific successes. The H-index creates a threshold that connects the N_p and N_c , combining productivity and effect. Put another way, a researcher will have an H-index if they have published H publications and each one has been referenced at least H times. Although the H-index was first designed to evaluate a student's academic performance, it can also be used to characterize the publication output of a nation or region, organization, or journal.

RESULT AND DISCUSSION

1.1. Overview of Publications on Tuberculosis

Our study provided new perspective on the scientific contribution of global countries to tuberculosis related research from 2019 to 2023. the Scopus algorithm identified 802 documents published by Global countries in the tuberculosis related field. Our study yielded the following results: 561 (70.0%) articles, 200 (24.9%) reviews, 14 (1.7%) editorials, 9 (1.1%) letter, 6 (0.7%) book chapter, and 12 (1.5%) others. Of the aforementioned publications, the majority speak English (n=790; 22.3%).

In general, the United States contribute 29.7% documents. In 2019, the number of article published by global countries increase dramatically, from 2019 to 2021. In two years, research related to chemokines in TB was lower compared to the previous year. In 2023 research focused on Biomarkers of immunology of TB.

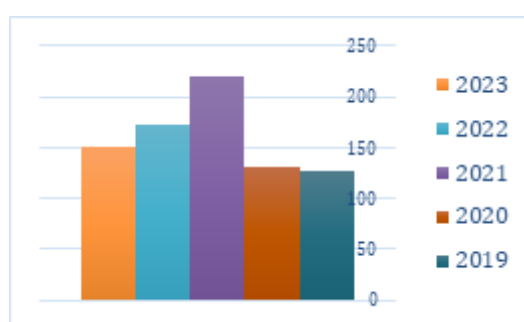


Fig. 1 Trends of publication articles on tuberculosis and chemokine from 2019 to 2023 by Global Countries.

The tuberculosis publishing trends in Global countries exhibited a gradual increase from 2019 to 2021. Tuberculosis and chemokine publishing trends globally exhibited a gradual increase from 1981 to 2023 (Fig. 1). In addition, the peak was 2021 published 220 following 2020 published 172 articles. The visualization of collaborating nations was shown in **Figure 2**. The relative size of the frames represents the number of collaborations. For example, the frame size of the United States is the largest among countries, in addition United Kingdom is larger than Germany, indicating that the United States (n=24) builds collaborative studies with most countries compared to other countries, following United Kingdom (n=23) builds more countries than Ghana (n=21).

The productivity among Global countries in research documents related to tuberculosis and chemokine was also ranked, with United States having the highest percentage. The top ten journals publishing articles related to chemokine in tuberculosis in Global countries were also listed (Table 2). The most documents were published at Frontiers In Immunology (n= 147; 18.3%), followed by Tuberculosis (n= 20; 2.5%), and Frontiers In Microbiology (n= 20; 2.5%). Also, the characteristics of papers published by Global countries with the highest number of citations in the last 5 years were listed in Table 3.

An author's term network visualization from Global countries in 5 years period of tuberculosis related research was illustrated in **Figure 3a**. A total of 802 distinct types of publications were found in the retrieved papers, 25 of which appeared more than 100 times. The following is an evaluation of the primary three central clusters: Terms pertaining to "macrophage," "nonhuman," and "immune response" are found in cluster 1 (shown in red); cluster 2 (shown in green) contains "tuberculosis", "human", "male", "female"; and cluster 3 (in blue) related to "tumor necrosis factor", "cytokine", "interleukine 10", "gamma interferon". VOSviewer software also designed colors to chemokine tuberculosis related terms based on publication years (**Figure 3b**). Terms that first occur in the early years are shown by the color purple, whereas terms that have emerged recently are indicated by the color yellow. The development of chemokine research in tuberculosis demonstrates a dynamic shift over time, with an emphasis on

“immunology”, “metabolism” in 2020; “controlled study”, “humans” interferon inducible pro” in 2021; “tuberculosis”, “cd4+ t lymphocyte”, “interleukin 6” in 2021. The institution from global nations with the highest rates of production in the chemokine tuberculosis from 2019-2023 were listed, and highlighting the prominent contributions of South Africa, US and UK.

DISCUSSION

Our research offered a fresh viewpoint on the scientific contribution of Global countries to chemokine in tuberculosis related research. In general, US contribute 29.7% of the worldwide chemokine production in areas connected to TB. The quantity of articles released by international nations skyrocketed in 2020, rising from 128 in 2019 to 220 papers. Following 2021, chemokine tuberculosis-related sectors generated by international nations were noted, suggesting that tuberculosis-related issues are becoming more and more important as concerns for human health.

In 2019, Unites States was contributes the most article with 40 documents. Article in 2019 most discussed the biomarker and signaling pathways of tuberculosis. Meanwhile, Hawerkamp et al reportef IL-26 activated macrophage can killing of *M. tuberculosis* (12). Also, in 2020 began to develop research on the BCG vaccine (13) and immunocompetent cells as therapeutic targets in TB (14).

It might be challenging to determine the weight or effect of publications directly in bibliometric study. Nonetheless, other research contended that examining the connection between article relevancy and journal significance could yield significant insights (15). Furthermore, as Table 3 illustrates, the top ten most referenced articles may offer insights into contemporary patterns, the evolving field of study subjects, and significant avenues for further investigation.

After 2021, Research focuses more on the development of the BCG vaccine through molecular targets in TB, and analysis of cytokine responses as TB vaccine biomarkers (16)(17)(18). Effective antimicroba In order to lower mortality and counteract the increasing prevalence of *Mtb* infection, interventions are needed. Furthermore, it has been suggested and researched as an alternative to treat MTB infection by repurposing already existing medications from natural sources. Furthermore, insilico techniques have been used to identify potential compounds that combat MTB (18)(19)(20).

The global study have been reported that drugs to against MTB cannot effective since the existence of Multidrug resistant TB (MDR TB). Improper use of antibiotics causes TB bacteria to become resistant, making treatment less effective. In order to treat the infection, natural antimicrobial ingredients are needed (21).

This study evaluates the trajectory and present status of research on tuberculosis published by international countries using bibliometric analysis. Nonetheless, certain limitations were noted that are also present in other bibliometric analyses. Because our research focused on articles indexed in Scopus, it's possible that our analysis missed any papers that contained the term "tuberculosis." Notwithstanding its limitations, this analysis is the first to offer a succinct summary of the chemokine in research related to tuberculosis that has been published by international nations.

Figure 1. Mapping of international cooperation amongst nations. Larger frame countries indicate comparatively more collaborative efforts.

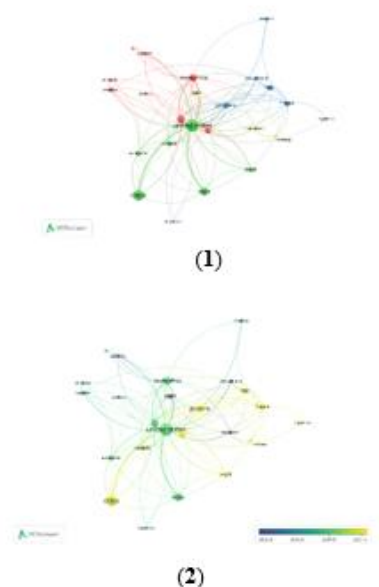


Figure 2. A network visualization of Co-occurrence network of terms extracted from articles published by Global country in TB related study in 4 decades. The minimum number of occurrences was set to 100 times

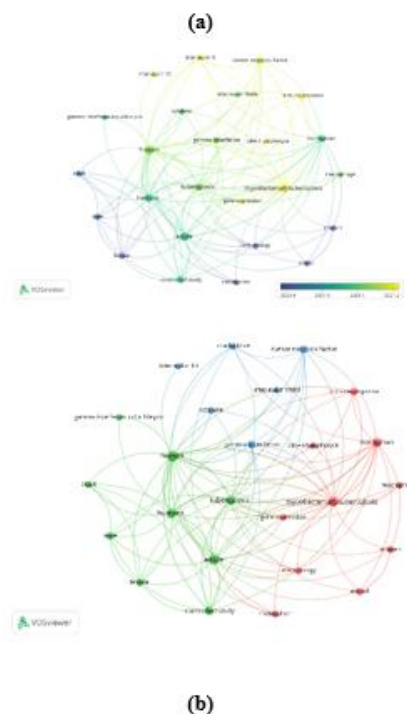


Figure 3. a network representation of the co-occurrence network of phrases taken from papers that Global Country produced in a four-decade study related to tuberculosis. One hundred occurrences was the minimum quantity that was required (a); Visualization overlay of a network representation of the co-occurrence network of phrases taken from papers that Global Country produced in a four-decade study related to tuberculosis. Blue denotes those that surfaced prior to those designated in yellow (b).

CONCLUSION

The objectives of the current study was to present an overview of the trend and new areas especially chemokine that has play role in the field of Tuberculosis disease. With 802 articles published in journals over the last five years, research production on *Mycobacterium tuberculosis*-related themes has improved in global countries. Prioritizing research on biomarkers and signaling pathways was done in the past. Nonetheless, study themes have evolved in recent years to examine vaccine target therapy MTB. The largest number of publications pertaining to chemokine TB is attributed to the United States. The results of this study can be used as a guide for continuing research in developing nations related to tuberculosis.

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