

Holistic Analysis of Cytokine and Cytokine Storm Researches in Scientific Literature: A Bibliometric Study of the Global Publications between 1980 and 2018

Abstract

Aim: Bibliometrics has been used for assessing and predicting trends in macro-health science and medical systems, especially in the field of cancer. Bibliometric and scientometric studies in the field of cytokines may guide further research in this field. Cytokines in particular cytokine storm has recently started to be highly discussed and studied in global viral infections. In the SARS-CoV-2 pandemic, cytokine storm was seen in many patients. In this study we want to present to perform bibliometric analysis of articles on cytokine and cytokine storm published in the academic literature during 1980 to 2018.

Methods: The bibliometric analysis was performed using the Thomson Reuters Web of Science database.

Results: A total of 232,606 articles were retrieved, 82.52% of which were original articles. The United States was the leading country by total publication number (n=84,426, 36.29%), followed by Japan (n= 21,983, 9.45%) produced the most literature on cytokine. Among the institutions identified, Harvard University (USA) contributed the most articles on cytokine. All authors and institutions in the top 10 contributor's lists were from the developed countries.

Conclusions: Researchers from the developing and least-developed countries should be encouraged to perform novel studies on cytokine. Cytokine studies are associated with the pathology and physiological variability of many diseases and may have beneficial results in the medical field. Cytokine and cytokine storm studies may be particularly useful in identifying the pathogenesis of global viral infections such as SARS-CoV-2, evaluating and developing new treatment strategies.

Keywords: Cytokine; Cytokine storm; bibliometrics; SARS-CoV-2; publication trend

What's already known about this topic?

- Bibliometric studies offer us the development of science in any subject in an easy and accessible way.
- Cytokine-cytokine storm studies have recently become important with COVID-19 pandemic.

What does this article add?

- Bibliometric analysis of cytokine-cytokine storm especially in infection diseases studies will be a useful guide to the researchers
- Cytokines are common research subjects in many medical fields such as Immunology, Clinical Biochemistry, Clinical Microbiology, Infectious Diseases and so multidisciplinary cytokine studies planned under the guidance of bibliometric analyses may offer scientific contributions to the development of many diagnostic and therapeutic protocols.

1. INTRODUCTION

Polypeptide cytokines produced and secreted by many cell types regulate immune and inflammatory events, including inflammation, cell growth, healing, and systemic response to injury [1]. Cytokines were initially called lymphokines because only lymphocytes were thought to be the source of cytokines [2]. It was later understood that monocytes also produced these factors, and the name of “*monocrine*” was coined [3]. Today, it is known that these mediators are not only secreted by lymphoid cells, and the name of “*cytokine*” is linked to more use. The classification of cytokines originates from many cells, resulting in a wide range. These include interleukins, interferons, tumor necrosis factor (TNF), chemokines, transforming growth factor (TGF), colony stimulating factors (CSF) [4]. Scientometrics or bibliometrics is the assessment of various qualitative and quantitative aspects of scientific literature in a certain field. Scientific studies evaluate characteristics and features of the authors, organizations and countries of the articles in the literature [5]. Bibliometric analyses evaluate academic studies in any subject in detail, allowing us to see the situation where scientific developments have come over the years in terms of panoromics and statistically. It also clearly demonstrates the influence and power of countries in the world in any scientific

matter. In this way it sheds light on the development of scientific policies [5,6,7]. For recent years, *cytokine* have been a popular topic that scientific researchers have measured and investigated quite frequently to explain immunological physiological and biochemical mechanisms in diseases. Although cytokine is a popular issue for explaining the pathogenesis of many diseases, the literature lacks a bibliometric article investigating scientific documents published in cytokine field. In the SARS-CoV-2 pandemic, which began in Wuhan, China in December 2019, cytokine storm was seen in some patients, and researchers have done quite a lot of work on cytokine storm. Cytokine storm was also seen in most patients with other global viral infections, such as MERS and SARS CoV-2 infections [8,9,10]. We can explain the cytokine storm a little over COVID-19 infection because it is related to the subject. Cellular entry of SARS-CoV-2 depends on the binding of S proteins covering the surface of the virion to the cellular ACE2 receptor, and on S protein priming by TMPRSS2, a host membrane serine protease. After entering respiratory epithelial cells, SARS-CoV-2 provokes an immune response with inflammatory cytokine production accompanied by a weak interferon (IFN) response. The pro inflammatory immune responses of pathogenic Th1 cells and intermediate CD14⁺ CD16⁺ monocytes are mediated by membrane-bound immune receptors and downstream signaling pathways. This is followed by the infiltration of macrophages and neutrophils into the lung tissue, which results in a cytokine storm [11,12,13].

In this study we aimed to evaluate bibliometric features of cytokine and cytokine storm literature covering a period during 1980 to 2018 and to the best of our knowledge, our study was the first to investigate bibliometric and scientometric networks of cytokine literature. We believe that this study will serve as a guide to future cytokine research, save time to focus on more important points, and make a scientific contribution by directing cytokine research.

2. MATERIALS AND METHODS

Web of Science databases (*Web of Science Core Collection, SciELO Citation Index, Russian Science Citation Index and Korean Journal Database*) were the main sources for our study. We included all documents including the keyword of “*cytokine*” published between 1980 and 2018. Papers produced in 2019 and 2020 were excluded. We produced infomaps by using GunnMap free web source [14]. Scientometric network graphics were created in a freeware named VOSviewer [15]. Hitit University Faculty of Medicine Clinical Research Ethics by the presidency of the board due to the design of the study board approval was not required.

3. RESULTS

3.1 General Features of Cytokine Literature

A total of 232,606 documents were indexed in cytokine literature between 1980 and 2018. The first document of cytokine literature published in 1980 was an original article titled “*Cytokine production invitro by lymphoid and nonlymphoid cells and partial-purification of a bone-resorbing factor*” written by Khan YA *et al.* [16] Annual productivity increased by year gradually and reached up to 12,631 items in 2018. With 12,654 documents, 2017 was top year in production (Figure 1). Most documents indexed in WoS databases were found to be original articles (82.523%) followed by reviews, meeting abstracts and proceeding papers (8.029, 6.975 and 4.169%, respectively; Table 1). The most studied areas in this area were immunology, molecular biology, cell biology and medicine (Table 2).

3.2 Authors, institutions and sources

All top ten authors were from China and the most prolific authors in this field were Zhang Y, Wang Y and Li Y (n=832, 831 and 729 items, respectively; Table 3). All most producer institutions were from the USA except only one from Japan, University of Tokyo. Harvard University was the top institution with 4741 documents (2.038%) followed by University of Pittsburgh, University of Michigan and National Cancer Institute (1.015, 0.942 and 0.931%, respectively; Table 4). *Journal of Immunology* covering 4.141% of all literature was the most contributor source title with 9633 documents (Table 5). The most cited manuscript in cytokine literature was an original article written by Oltvai ZN, Milliman CL and Korsmeyer SJ published in 1993 in the journal of Cell titled “*Bcl-2 heterodimerizes in vivo with a conserved homolog, Bax, that accelerates programmed cell death*”[17].

3.3 Productivity of countries

The United States of America (USA) covered 38.01% of all cytokine literature with 88,426 articles followed by Japan, Germany, China and the United Kingdom (UK) (n=21,983, 20,744, 20,375 and 15,627 items, respectively). China was the only developing country among top ten countries producing articles in cytokine literature (Figure 2). Documents were published all around the world except certain regions of Africa, Mongolia and Papua New Guinea (Figure 3).

3.4 Scientometric Networks

We performed scientometric network analyses by downloading indexed data of all indexed documents in WoS Core Collection between 1980 and 2018. The most indexed keywords in

the literature of cytokine were found to be “*cytokine*”, “*inflammation*”, “*apoptosis*”, “*macrophage*” and “*IL-6*” (Table 7). Scientometric network analysis revealed a “starburst” pattern in which the keyword of “*cytokine*” centered (Figure 4). The USA was detected to be the most collaborative country in cytokine studies followed by China, Japan, South Korea, Germany, the UK and Italy (Figure 6). The top collaborative institutions were Harvard University (USA), Shanghai Jiaotong University (China), University of São Paulo (Brazil) and University of Melbourne (Australia) (Table 7).

3.5 Collaborations

The USA was the most collaborating country with 17,922 indexed and 415,864 cited items (tls=10008) followed by Germany, the UK, China, France and Italy (tls=4286, 3993, 2952 and 2211, respectively; Figure 5). In scientometric analysis of the organizations, the most collaborating institutions were detected to be Harvard University, University of Pennsylvania, University of California, University of Washington and University of Pittsburg (total link strength= 962, 549, 548, 513 and 494, respectively; Figure 6).

3.6 An update of scientometric analysis for “cytokine storm”

We also analyzed the term of “cytokine storm” in WoS Core Collection. We evaluated a timeline including papers produced between 1993 and 2020 till the day of completing scientometric analysis of this article (September 4, 2020). First documents in this field were reported in 1993 [17]. A total of 1673 articles was retrieved from the database. The most studied areas were Immunology, cell biology, medicine, pharmacology, and hematology (24.5, 9.6, 8.9, 8.0 and 7.8%, respectively). The peak year in production was 2020 with 621 items (37.1% of total literature). Original articles covered 60.968 of the literature. The USA was leading country with 635 papers followed China, the UK, Italy, Japan, Germany (37.9, 16.0, 8.1, 7.2, 7.0 and 6.7%, respectively). English was the main language of the literature (97.9%). The most contributor institutions were University of Pennsylvania (USA), Chinese Academy of Sciences (China), Harvard Medical School (USA), Huazhong University of Science and Technology (China) and Emory University (USA) (1.554, 1.315, 1.315, 1.255 and 1.195%, respectively). Zhang L from Huazhong University of Science and Technology, Wuhan, China was found as the most prolific author with 18 articles. The most contributor source titles were *Frontiers in Immunology*, *Journal of Immunology*, *PLOS One*, *Blood* and *Journal of Medical Virology* (2.929, 2.57, 1.793, 1.614 and 1.494%, respectively). H-index of the literature was measured as 81 and total number of citations was 33,644 (30,059 without self-citations). An original article titled “Cytokine storm in a phase 1 trial of the anti-CD28

monoclonal antibody TGN1412” by Suntharalingam G *et al.* published in 2006 was the most cited document with 1230 citations [18]. The most used keywords in “cytokine storm” literature were “*COVID-19*”, “*cytokine storm*”, “*SARS-CoV-2*”, “*coronavirus*”, “*cytokine(s)*”, “*inflammation*”, “*tocilizumab*”, “*sepsis*”, “*IL-6*” and “*pneumonia*” (Figure 7). The most collaborative countries were the USA, the UK, Germany, China and France (total link strength= 373, 170, 142, 142 and 132, respectively). The most cooperative institutions were Harvard Medical School (USA), University of Pennsylvania (USA), University of Minnesota (USA), University of Pittsburgh (USA) and Emory University (USA) (Total link strength=57, 40, 35, 34 and 30, respectively).

4. DISCUSSION

Cytokine and cytokine storm studies have been of interest for many years by researchers to identify biochemical mechanisms, intercellular communication and interaction, inflammation, cellular immunity in the body [19]. Cytokine studies are particularly important for the evaluation of infectious diseases, and the phenomenon of cytokine storm causes a prognosis that makes treatment difficult in viral infections and fights the immune system against the body. The pandemic, which began in December 2019, was caused by a cytokine storm, the biggest challenge in Coronavirus treatment. Mortality in patients with cytokine storm was higher in the COVID-19 pandemic, and these patients were more likely to undergo intubation and intensive care processes [20,21,22,23,24]. From this point of view, cytokine studies have become quite important, especially in the evaluation of global viral infections. Accurate evaluation of cytokine studies may offer benefit to developing new strategies for the treatment of this type of global viral infections, and bibliometric analysis of cytokines may be time-saving and guiding researchers on this path. The role of cytokines in the pathogenesis of many diseases contributes to the development of diagnostic and treatment strategies. A bibliographic assessment of cytokine research can offer a panoramic view of the academic adventure on the subject. Particularly, with the identification, detection and measurement of different cytokine molecules in biological materials, researchers have increased their interest in this subject. The development of methods and kits used in the measurement of cytokine molecules is an economic and important factor determining the interest of scientists in research. From this perspective, the level of development of countries and national income per capita is an important factor in determining the interest of researchers. This bibliometric analysis may be a guiding role for researchers in future cytokine studies. The present analysis can help and guide in many subjects, such as which keywords researchers will use the most, which authors will benefit the most, which journals are most interested in cytokine studies.

Cytokine bibliometric studies with these positive aspects can be timesaving for researchers and offer the possibility of an ergonomic study. The researchers' interest in cytokine studies began in the early 1990s and is still increasing. The increase in diversity in cytokine molecules and its relevance to many pathologies may explain this logarithmic literature increase. The country that produced the most literature on the subject is the United States, followed by Japan, Germany, China and other European countries. There are no African countries in the top ten. When we examine the keyword network, it is seen that cytokines are associated with many diseases and pathologies. However, cytokines are more associated with inflammation, apoptosis, oxidative stress, immune system cells, and molecules secreted from immune system cells, autoimmune diseases. The 20 most used keywords provide insight into the range of cytokine studies. Keyword network analysis gives us concrete and clear information about which pathologies cytokines are associated with, which subjects are studied together, which diseases and groups of patients are investigated. With this aspect, keyword network analysis can be a very useful guide for researchers who will study cytokine. In country network analysis, the United States of America and China are the two countries that dominate the cytokine literature. European countries and Japan are other countries influential in country network analysis. The Institution network analysis shows that USA and Chinese universities are the institutions that produce the most literature. It is expected to contribute more to the literature from countries producing ELISA kit on cytokine molecules. When we examine the literature on cytokines, we see that the most studied type of document is the original article. The journal names were found to be informative on cytokine-related research areas such as immunology, biological chemistry, allergy, leukocyte biology. Particularly, Chinese authors were seen to dominate the top ten list in cytokine-related studies. However, the top ten institutions by number of publications in cytokine literature was dominated by USA universities. The most cited article on cytokine related was published in 1993 by Oltvai et al. published by the name 'Bcl-2 heterodimerizes in vivo with a conserved homolog, Bax, that accelerates programmed cell death'[17].

In conclusion, although there has been a growing interest in cytokine studies in recent years, the fact that our study was the first in the bibliometrics of cytokine-cytokine storm and that there was no other study to compare was indicative of the inadequacy of the statistical literature in this area. We found a moderate correlation with the number of publications and level of development of countries. Researchers in low-income countries should to be supported and encouraged to carry out cytokine studies. Cytokine-cytokine storm studies may be particularly useful in identifying the pathogenesis of global viral infections such as

MERS, SARS-CoV and SARS-CoV-2 infections, evaluating and developing new treatment strategies.

DISCLOSURES

The authors report no conflict of interest

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Figure Legends:

Figure 1: Record count of cytokine literature by year

Figure 2: Top 10 countries producing cytokine literature

Figure 3: Global cytokine publication density according to the countries

Figure 4: Keyword network related with cytokine researches

Figure 5: Cooperation network among countries

Figure 6: International cooperation network among institution

Figure 7: Keyword map of cytokine storm researches