

# Analysis of cytokine and COVID-19 associated cytokine storm researches in scientific literature: A bibliometric study

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## Abstract

**Objective:** In this article, we aimed to perform bibliometric analysis of articles on cytokine and cytokine storm published in the academic literature during 1980 to 2018-2020.

**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 of America (USA) 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.

**Conclusion:** Researchers from the developing and underdeveloped 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 useful particularly in identifying the pathogenesis of global viral infections such as SARS-CoV-2, evaluating and developing new treatment strategies.

**Keywords:** Cytokine, cytokine storm, COVID-19, bibliometric, publication trend.

## INTRODUCTION

Polypeptide cytokines are 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 commonly used. 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) and 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 panoramics and statistics. It also clearly demonstrates the influence and power of countries in the world in any scientific issue. In this way, it sheds light on the development of scientific policies (5-7). In recent years, *cytokine* has 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 the field of cytokine. In the SARS-CoV-2 pandemic, which began in Wuhan, China in December 2019, cytokine storm was observed 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 (8-10). 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 proinflammatory 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 (11-13).

In this study we aimed to evaluate bibliometric features of cytokine and cytokine storm literature covering a period during 1980 to 2018-2020 and, to the best of our knowledge, our study was the first to investigate bibliometric networks of cytokine literature. We believe that this study will serve as a guide to future cytokine researches, save time to focus on more important points, and make a scientific contribution by directing cytokine research.

## 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 key word of “*cytokine*” published between 1980 and 2018. Bibliometric analysis of cytokine storm literature from 1993-2020 was added to the article when it began to appear frequently in patients in the COVID-19 pandemic that occurred during our study. We produced infomaps by using GunnMap free web source (14). Scientometric network graphics were created in a freeware named VOSviewer (15). Clinical Research Ethics by the presidency of the board due to the design of the study board approval was not required.

RESULTS

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; Table1). The most studied areas in this area were immunology, molecular biology, cell biology and medicine (Table 2).

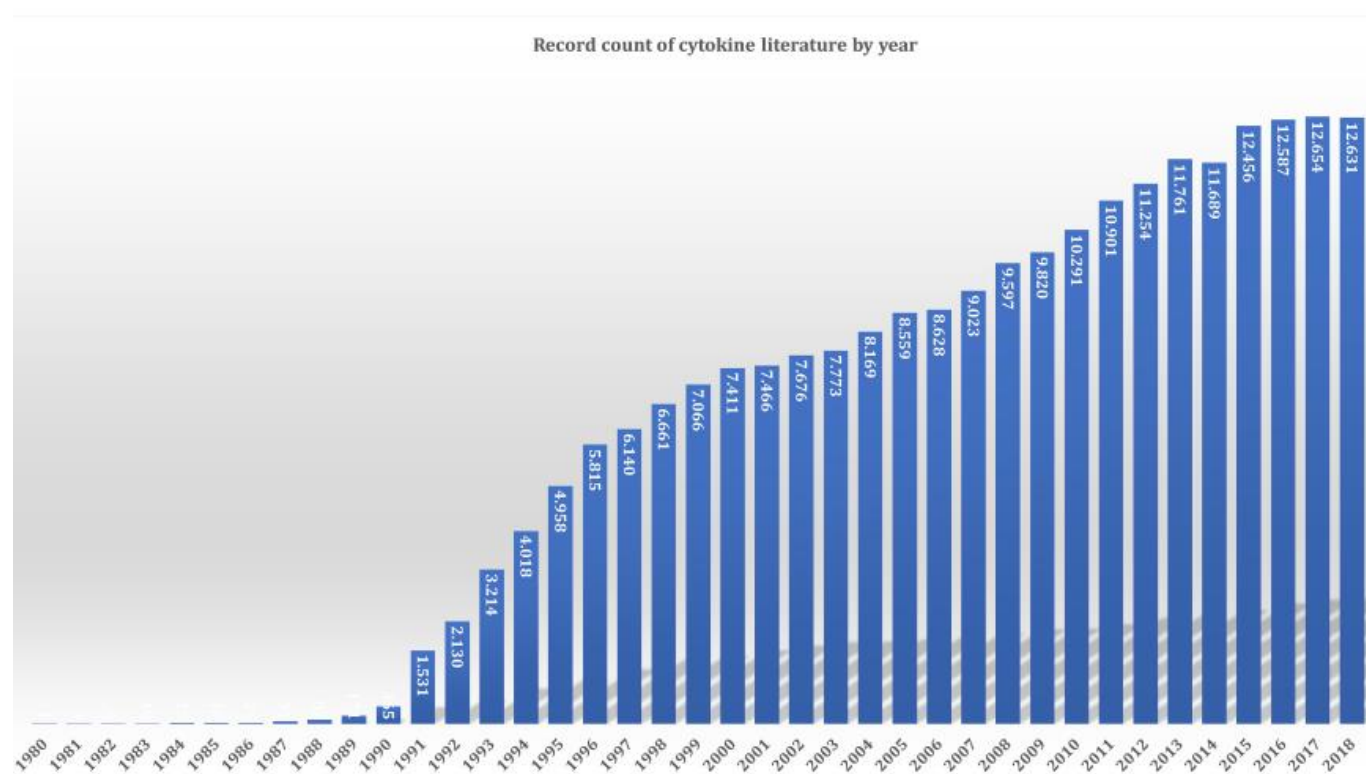


Figure 1: Record count of cytokine literature by year

**Table 1.** Types of publications of cytokine literature between 1980 and 2018<sup>a</sup>

Document Type	Number	% <sup>a</sup>
Original article	191,953	82.523
Review	18,675	8.029
Meeting abstract	16,224	6.975
Proceeding paper	9,699	4.169
Editorial material	1,815	0.78
Book chapter	1,603	0.689
Letter	824	0.354
Note	741	0.319
Correction	350	0.15
Retracted publication	123	0.053
News	63	0.027
Book	6	0.003
Biographical item	2	0.001
Book review	2	0.001
<b>Total</b>	<b>232,606</b>	<b>100</b>

<sup>a</sup>Total percentage may exceed 100%; certain items were included in more than one category.

**Table 2.** The first 10 research areas by publications in cytokine literature between 1980 and 2018

Research Areas	Number of publications	%
Immunology	66,098	28.416
Molecular Biology	28,043	12.056
Cell Biology	25,824	11.102
Medicine	16,077	6.912
Oncology	15,112	6.497
Pharmacology	14,454	6.214
Hematology	13,081	5.624
Neurosciences	12,242	5.263
Endocrinology	7,944	3.415
Surgery	7,683	3.303

**Table 3.** The top ten authors by record count in cytokine literature between 1980 and 2018

Author	Institution	Country	Record Count	%
Zhang Y	Shanghai Jiaotong University	China	832	0.358
Wang Y	Shengjing Hospital of China Medical University	China	831	0.357
Li Y	The First Affiliated Hospital of China Medical University	China	729	0.313
Liu Y	China Agricultural University	China	699	0.301
Li J	Capital Medical University	China	676	0.291
Wang J	Tianjin First Central Hospital	China	603	0.259
Zhang J	Mingzhou Hospital of Zhejiang University	China	584	0.251
Zhang L	Shanghai Medical College of Fudan University	China	570	0.245
Wang L	The Second Hospital of Jilin University	China	527	0.227
Wang H	China Medical University	China	507	0.218

**Table 4.** The top ten institutions by number of publications in cytokine literature

Organizations	Country	Document number	%
Harvard University	USA	4741	2.038
University of Pittsburgh	USA	2360	1.015
University of Michigan	USA	2192	0.942
National Cancer Institute	USA	2166	0.931
University of Pennsylvania	USA	2133	0.917
University of Texas	USA	2008	0.863
University of Tokyo	Japan	1972	0.848
University of California	USA	1892	0.813
National Institute of Allergy and Infectious Diseases	USA	1799	0.773
University of Washington	USA	1706	0.733

**Table 5.** The top ten source title of cytokine literature according to the number of published documents

Journal Name	Number of Publications	%
Journal of Immunology	9633	4.141
PLOS One	5018	2.157
Blood	3342	1.437
Journal of Biological Chemistry	3144	1.352
Cytokine	2736	1.176
Infection and Immunity	2299	0.988
European Journal of Immunology	2104	0.905
FASEB Journal	1907	0.820
Journal of Allergy and Clinical Immunology	1848	0.794
Journal of Leukocyte Biology	1768	0.760

### Authors, institutions and sources

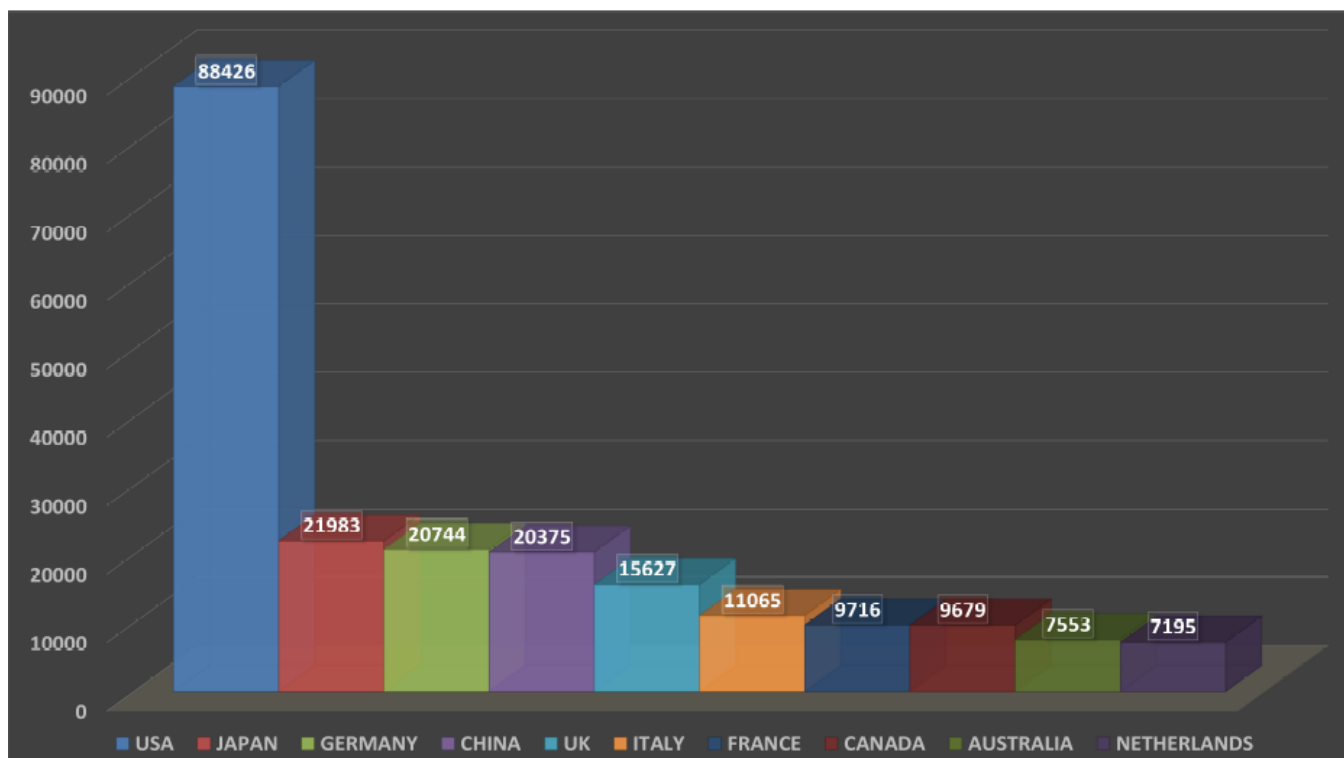
All top ten authors were from China and the most prolific authors in this field were Zhang Y, Wang Y and Li Y (n=832,831 and 729 items, respectively; Table 3). All top producer institutions were from the USA except only one from Japan, University of Tokyo. Harvard University was the top institution with 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) ( Table 6).

**Table 6.** The 20 most cited manuscripts in the cytokine literature between 1980 and 2018

Article	Author	Journal Name	Total Citation	Year
Bcl-2 Heterodimerizes In-Vivo with A Conserved Homolog, Bax, That Accelerates Programmed Cell-Death	Oltvai, ZN <i>et al.</i>	Cell	4945	1993
A Toll-like receptor recognizes bacterial DNA	Hemmi H <i>et al.</i>	Nature	4464	2000
Interleukin-10 and the interleukin-10 receptor	Moore KW <i>et al.</i>	Annual Review of Immunology	4286	2001
Inflammation and cancer: back to Virchow?	Balkwill F <i>et al.</i>	Lancet	4278	2001
Recognition of double-stranded RNA and activation of NF-kappa B by Toll-like receptor 3	Alexopoulou L <i>et al.</i>	Nature	3964	2001
Osteoprotegerin ligand is a cytokine that regulates osteoclast differentiation and activation	Lacey DL <i>et al.</i>	Cell	3798	1998
Functional diversity of helper T lymphocytes	Abbas AK <i>et al.</i>	Nature	3487	1996
Biologic basis for interleukin-1 in disease	Dinarelli CA	Blood	3300	1996
Interleukin-10-Deficient Mice Develop Chronic Enterocolitis	Kuhn R <i>et al.</i>	Cell	3159	1993
How cells respond to interferons	Stark GR <i>et al.</i>	Annual Review of Biochemistry	3068	1998
Interleukin 17-producing CD4(+) effector T cells develop via a lineage distinct from the T helper type 1 and 2 lineages	Harrington LE <i>et al.</i>	Nature Immunology	2999	2005
The orphan nuclear receptor ROR gamma t directs the differentiation program of proinflammatory IL-17(+) T helper cells	Ivanov I <i>et al.</i>	Cell	2952	2006
A Protein-Kinase Involved in the Regulation of Inflammatory Cytokine Biosynthesis	Lee JC <i>et al.</i>	Nature	2928	1994
STATs and gene regulation	Darnell JE	Science	2892	1997
Inflammation and Alzheimer's disease	Akiyama H <i>et al.</i>	Neurobiology of Aging	2864	2000
The expanding universe of T-cell subsets: Th1, Th2 and more	Mosmann TR <i>et al.</i>	Immunology Today	2846	1996
IL-17 and Th17 Cells	Korn T <i>et al.</i>	Annual Review of Immunology	2810	2009
A Cell Initiating Human Acute Myeloid-Leukemia After Transplantation into SCID Mice	Lapidot T <i>et al.</i>	Nature	2765	1994
Development of Th1 CD4+ T-Cells Through IL-12 Produced by Listeria-Induced Macrophages	Hsieh C <i>et al.</i>	Science	2737	1993
Vascular endothelial growth factor (VEGF) and its receptors	Neufeld G <i>et al.</i>	FASEB Journal	2707	1999

### Productivity of countries

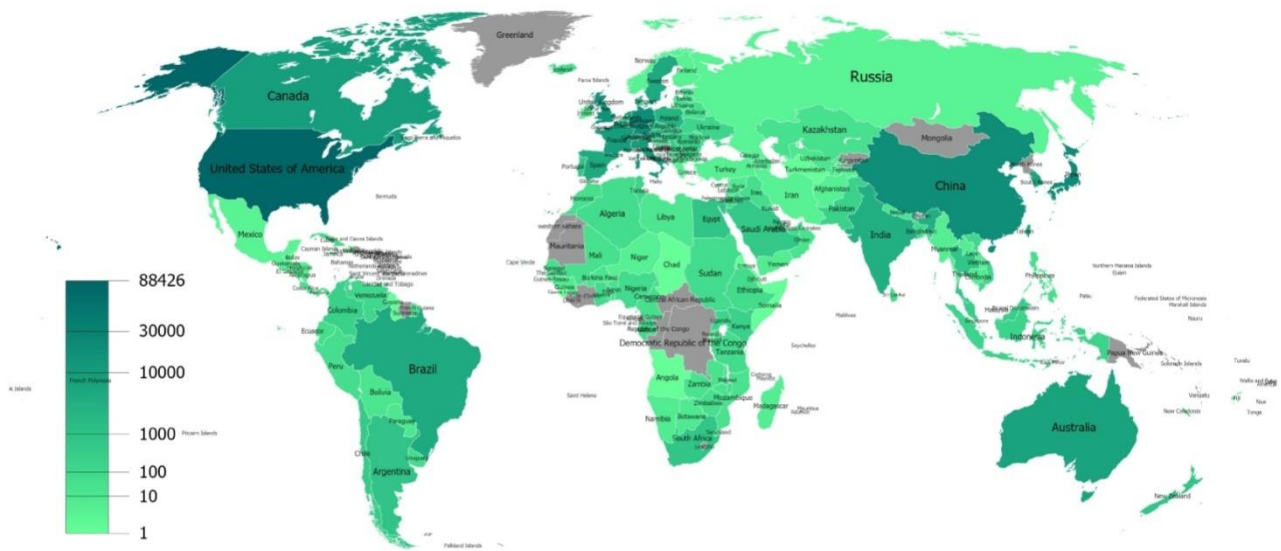
The USA covered 38.01 % of all cytokine literature with 88,426 articles followed by Japan, Germany, China and the United Kingdom (UK) (n=21,983, 20,744, 20,375 and 15,627 items, respectively). China was the only developing country among top ten countries producing articles in cytokine literature (Figure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



**Figure 2:** Top 10 countries producing cytokine literature

### 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 4).

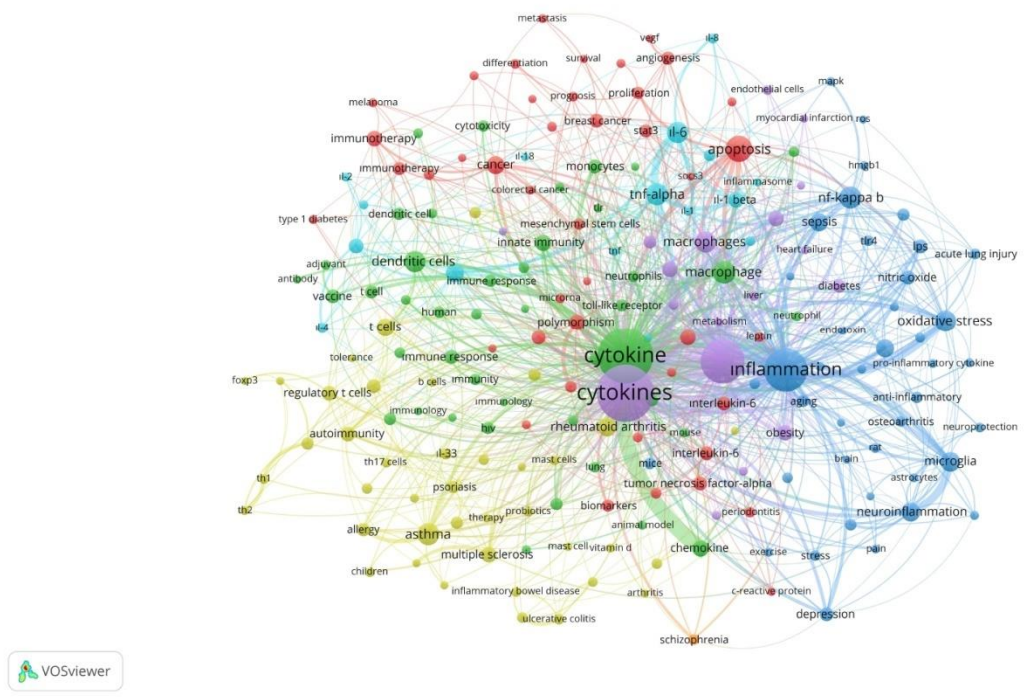


**Figure 3:** Global cytokine publication density according to the country

**Table 7.** The 20 most used keywords in cytokine literature between 1980 and 2018

Rank	Keyword	Total link strength	Occurrences (per 100,000 items)
1	Cytokine(s)	8861	3860
2	Inflammation	6053	2534
3	Apoptosis	2013	904
4	Macrophage(s)	1833	715
5	IL-6	1706	615
6	TNF- $\alpha$	1665	653
7	NF- $\kappa$ B	1624	656
8	Asthma	1596	677
9	Microglia	1528	551
10	Oxidative stress	1506	639
11	Dendritic cell(s)	1332	611
12	Neuroinflammation	1288	511
13	Cancer	1203	444
14	IL-10	1199	448
15	T cell(s)	1194	445
16	Lipopolysaccharide	1101	474
17	Chemokine(s)	1100	384
18	Rheumatoid arthritis	1073	505
19	Sepsis	1052	461
20	IL-1 $\beta$	983	339





**Figure 4:** Keyword network related with cytokine researches

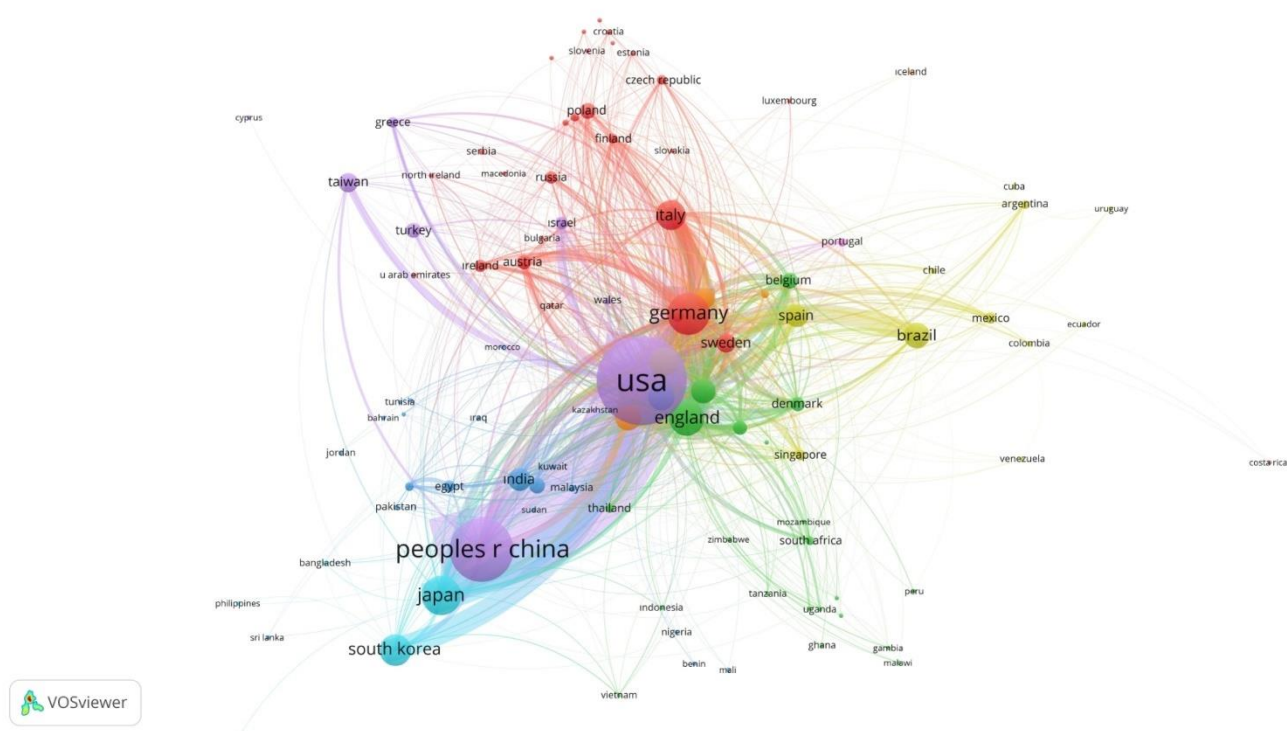
**Collaborations**

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).

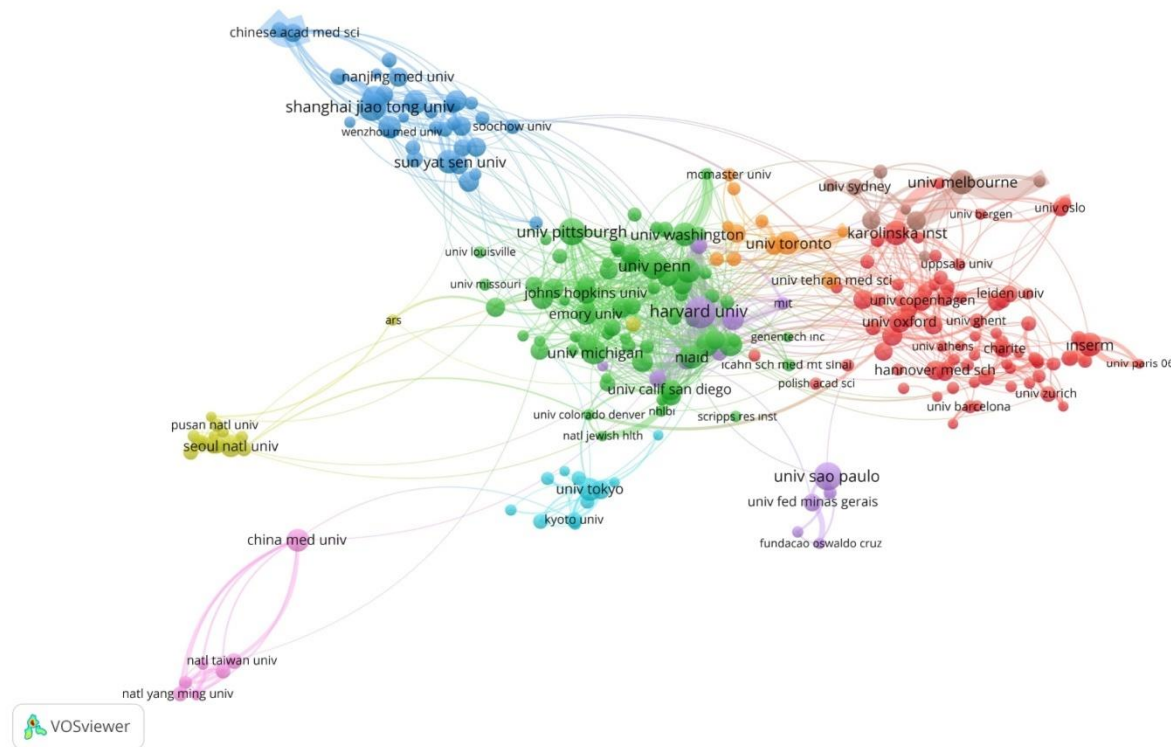
**An update of scientometric analysis for “cytokine storm”**

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 by China, the UK, Italy, Japan and 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 contributing 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 leading 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).



**Figure 5:** Cooperation network among countries

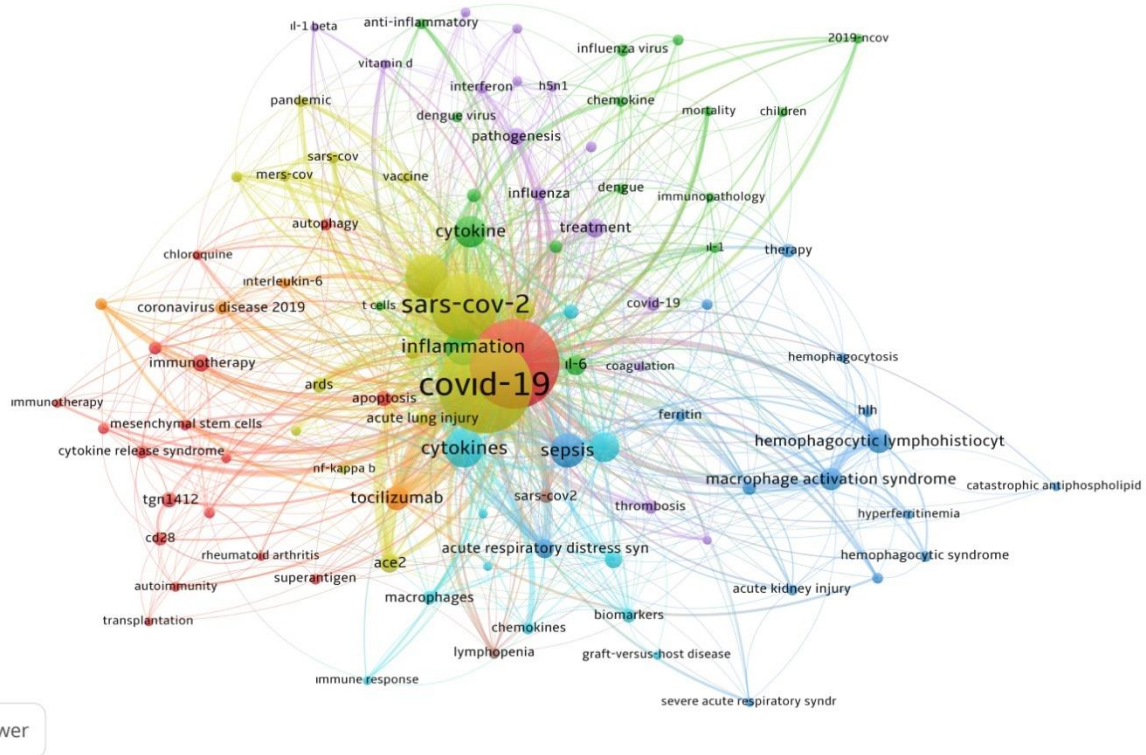


**Figure 6:** International cooperation network among institution

## 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 rate 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 (20-24). 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 develop 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 play a guiding role for researchers in future cytokine studies. The present analysis

can be helpful and guiding in many subjects, such as which keywords researchers will use commonly, which authors will benefit the most, which journals are most interested in cytokine studies.



**Figure 7:** Keyword map of cytokine storm researches

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 has begun 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 the keyword network is investigated, 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 in to 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 USA 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 the USA and Chinese universities are the institutions that produce the most abundant 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 common type of the documents are original articles. 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 cytokines 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).

**Limitations:** The present research has a limitation. We did not utilize databases such as PubMed, Scopus, or Google Scholar, which contain more publications than WoS. We preferred only WoS index for literature review because it is the most reliable database indexing the journals with high-impact factors and covering the oldest publications.

## 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 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.

**Conflict of interest:** The author declares that there is no conflict of interest.

**Financial disclosure:** No funding was received in support of this study.

**Peer-review:** Externally peer-reviewed.

**Authorship contributions:** Concept; HHKS, YB, EŞ - Design; HHKS, YB - Supervision; EŞ - Funding; HHKS - Materials; EŞ - Data collection &/or processing; EŞ - Analysis and/ or interpretation; HHKS - Literature search; HHKS, YB - Writing; HHKS, YB, EŞ Critical review; HHKS, YB, EŞ.

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