



Minireview

Global research trends of interleukin-6 in SARS-CoV-2 infection

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Received 27 February 2022; revised 23 April 2022

IL-6 levels are significantly elevated in COVID-19 patients and are associated with poor clinical outcomes. Inhibiting IL-6 is thought to be a unique therapeutic strategy for the control of dysregulated host responses in SARS-CoV-2. The present study focuses on evaluating the research productivity of IL-6 level in SARS-CoV-2 infection using various bibliometric indicators and analysed 4510 research papers related to IL-6 levels in SARS-CoV-2 from the Scopus database and VOS Viewer tool applied for visualization. The results revealed that ascendant trends in the publications and USA, China and Italy have secured top three position in numbers of publications. Study observed that “Dagna L.” received top prolific author rank. Article entitled “Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China” received maximum of 15364 total citations, whereas “Frontiers in Immunology” and “Journal of Medical Virology” secured in top two highly productive journals in the subject with extreme link strength. With regard to organisation, “Tongji Medical College-China” reported highly dynamic organization. “COVID-19”; “SARS-CoV-2”; “Interleukin” received maximum occurrences with high link strength. In view of global mounting public health issue of COVID-19, primarily due to increased viral transmissibility and associated cytokine storm, the present study will helpful for the medical professionals to know the research trends and also library authority for updating collection development policy in the specific subject domains.

Keywords: COVID-19, Interleukin-6, Mapping, SARS-CoV-2, Scientometrics

Introduction

The novel severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2), a zoonotic virus; causing coronavirus disease-2019 (COVID-19) is still dispersing globally with fatal consequences¹. COVID-19 spread hastily after the index case were reported in Wuhan city of China, on December 2019², and had been documented in 222 nations as of June 22, 2021 (Coronavirus Update (Live): 752,854 Cases and 36,230 Deaths from COVID-19 Virus Outbreak - Worldometer, n.d.). Hitherto, the nation's utmost affected by COVID-19 include the United States, India, Brazil, and France. As of June 22, 2021, World Health Organization (WHO) data shows that there were 179,697,951 total cases and about 3,891,349 deaths³. The ACE-2 (angiotensin converting enzyme 2) receptor has been identified as a cellular target for binding of SARS-CoV-2 virus⁴ and has ten-to-twenty-fold higher affinity for the ACE-2 receptor than other members of family Coronaviridae.

SARS-CoV-2 infection present as symptomless, mild to moderate pulmonary/non-pulmonary symptoms, or severe pneumonia and acute respiratory distress syndrome (ARDS) with multiorgan damage. SARS-CoV-2 infection often leads to a series of long-term pathologies with unprecedented consequences, entitled as long covid or post-covid syndrome⁵. These multifaceted clinical presentations are indicative that SARS-CoV-2 induces a reaction from the host that causes a dysregulated immune-inflammation⁶. Hyperactivation of the humoral immune response, particularly interleukin-6 (IL-6), appears to be a crucial moderator for shock, ARDS and cytokine storm, conferring to the immunologic evidence of critical SARS-CoV-2 patients^{7,8}.

Ever since discovery of Interleukin-6 it has been one of the core research areas for the researchers in the field of immunology across the globe. Interleukin-6 (IL-6) plays a diverse critical protagonist in the immunological and inflammatory responses against infection, besides serving as a key regulator of the coagulation cascade. IL-6 is secreted by a variety of cell types in response to inflammation, infection,

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and oncogenesis^{9,10}. Activation of numerous nuclear transcription factors like nuclear factor for IL-6 (NF-IL-6), nuclear factor- κ B (NF- κ B), and hypoxia inducible factor-1 α (HIF-1 α) regulate the production of IL-6¹¹. The pro-inflammatory effects of IL-6 are well-known. But at the other contrary, pleomorphic IL-6 has regenerative and anti-inflammatory properties, which is vital for clearance of pathogen¹². IL-6 level has been found to be elevated in severe conditions like as ARDS, sepsis and even in SARS-CoV-2 infection. Identification of SARS-CoV-2 virus by immune system activates humoral and adaptive immune responses, results in an overabundance of cytokines, especially IL-6, which causes a cytokine storm or systemic inflammatory response syndrome (SIRS)¹². Higher level of serum IL-6 in COVID-19 patients who developed ARDS compared to those who did not develop ARDS [difference of 0.93 pg/mL (95% CI, 0.07-1.98 pg/mL and $P=0.03$)] in Wuhan city of China have also been reported¹³. When they compared patients with ARDS who died to those who survived, the value of IL-6 was considerably higher in those who died [difference of 3.88 pg/mL (95% CI = 2.20-6.13 pg/mL and $P < .001$)]. higher level of IL-6 in severe cases (25.2 pg/mL) than non-severe cases (13.3 pg/mL) of COVID-19 and they concluded that SARS-CoV-2 virus dysregulates immune response by acting on T-lymphocytes¹⁴. In one of the study it was concluded that IL-6 could be a potential target to predict severity and outcome in patients of COVID-19¹⁵. Furthermore, COVID-19 patients with increased C-reactive protein (CRP) who were treated with an IL-6 inhibitor had a considerably lower risk of mortality and unfavourable clinical consequences were also observed¹⁶. Hence, IL-6 inhibitor can be used as promising immunotherapeutic option in patients of COVID-19 with severe complications.

India would be celebrating the glorious 75 years of its independence in the year 2022. In these 75 years of independence Indian researchers have proved themselves across the world across the globe in every scientific discipline. However, even before independence Indian scientists was actively engaged in their work and have accomplished exception work. In the field of medicine contribution of Indian science is world known since Vedic era which is considered to be between 4000 to 900 BCE. However, during 1000 BCE Ayurveda held a strong position and it is still in practice at wide level. Charaka and Shushruta are considered as founding fathers of science of

healing. In the field of immunology India started research work after 21 year of Independence in 1968 at All India Institute of Medical sciences, New Delhi which was converted by group of biochemists. The earlier research in the field of immunology was confined to development of contraceptive vaccines, MHC (Major histocompatibility complex) and polymorphism. Cell mediated immunity related work was initiated by Indira Nath and worked on immune suppression due to prostaglandins, leukotrienes and Interleukin¹⁷. Cytokine, India's first publication related to Interleukin-6 indexed in science citation indexed database appeared in the year 1991 which rose to 231 publications count in the year 2021. Up to year 2021 there are 2042 Indian research publications on Interleukin (Fig. 1).

No specific study has focused on the subject of interleukin (IL-6) in SARS-CoV-2. However some studies of COVID-19 research output of India¹⁸ and International collaboration in COVID-19 by Indian researcher¹⁹ have been studied earlier. Hence, the present study attempted to measure the research productivity in this emerging topic.

Objectives

The present study has considered following objectives:

1. To study the year-wise research output of India and World in Interleukin-6.
2. To identify most prolific authors and highly cited documents in the realm of Interleukin and COVID-19 and highly cited publications on Interleukin.
3. To understand the distribution of top productive journal titles and highly productive organizations in the field of Interleukin and COVID-19.
4. To understand network visualization of co-authorship, co-occurrence of keywords, citation analysis and bibliographic coupling analysis in the area of Interleukin and COVID-19.

Materials and Methods

We retrieved data on interleukin and COVID-19 from the Scopus Database which is widely accepted bibliographic database for conducting bibliometric research. The data is collected on the domain of interleukin by using the related key words. The search was used : (TITLE-ABS-KEY ("interleukin") AND TITLE-ABS-KEY ("COVID-19") OR TITLE-ABS-KEY (" COVID-19 ") OR TITLE-ABS-KEY (" SARS-CoV-2")) from Scopus bibliographic database

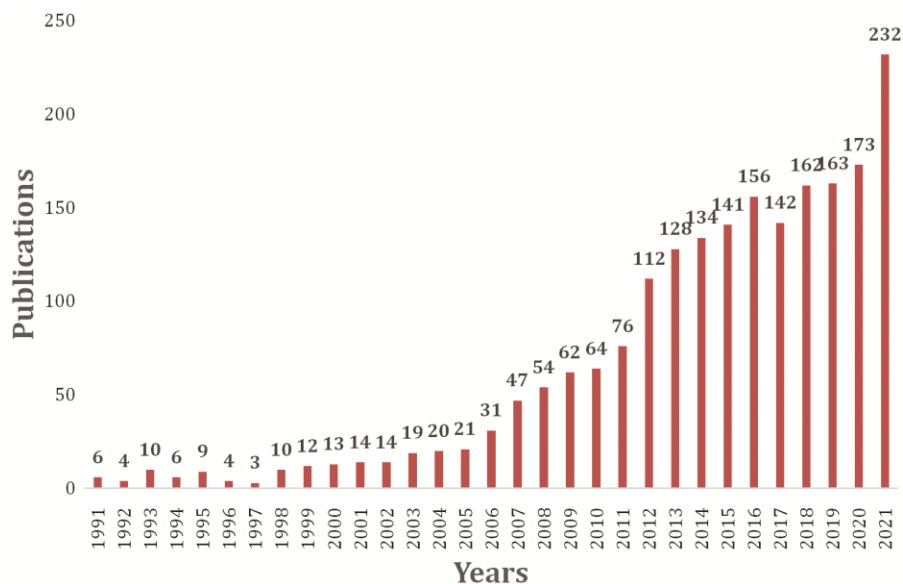


Fig. 1 — India's year-wise publication on IL-6

and due care has been taken while, in the process of retrieving data from Scopus in terms of search criteria like selection of keywords, removing duplication of documents, filtration of types of documents and finally retrieved total 4510 articles on 15th June 2021 on subject domain interleukin and considered in the final study for basic bibliometric analysis and network visualization. As the Interleukin and COVID-19 is an emerging topic; consequently, associated articles were found only from the year 2019. The present study used VOS viewer to study the relationship and network visualization, as the tools is widely accepted in the visualization evaluation in bibliometric study. We also carried out search in Web of science core collection to find Indian research output in interleukin-6 during 1945-2021. All these data were exported in MS-Excel and were normalized to further analyse the data for the study. All the variants of Author's, Institutions and Other anomalies were normalized to standard names in order to avoid any discrepancies in the analysis.

Results and Discussion

Distribution of Year-wise and country-wise scientific growth of research production

The interleukin and COVID-19 is an emerging area and study observed that first publication occurred in the year 2019. Study observed total 02 publications in year 2019, followed by a massive surge of 3116 publications in the year 2020 and total 1392 publications in year 2021 till June 2021 with total 03,

95517 and 3453 citations reported, respectively, from year 2019 to 2021. Overall, total 4510 articles have been published in this subject domain. Study analysed country-wise total publications in the field of interleukin and COVID-19., it was observed that USA, China and Italy have secured top three positions with total 1373, 945 and 804 publications, respectively, in the field of Interleukin and COVID-19. UK and India were secured fourth and fifth positions with 393 and 357 research articles, respectively, in the country classification. Canada (176 articles) is geographically large country but contributed less scientific publications whereas Italy is a geographically small country but contributed significantly in this domain with total 804 articles,

Distribution of most prolific authors

Table 1 illustrates the top ten most prolific authors in the domain of interleukins and COVID-19 who produced maximum number of publications. Result revealed that Dagna, L. contributed total 19 articles in the domain followed by Cavalli G. and Liu, L and Tabarsi, P. with 15, 14 and 13 publications, respectively. It was also observed that ranked three author in the list i.e. Liu, L, has received the maximum citations of 940 and secured top ranked under total citations criteria followed by Netea, M.G. and Conti, P. with 924 and 807 total citations, respectively. Correspondingly, it was also perceived that four authors from Italy and two authors from Iran has represented under most prolific author category.

Table 1 — Distribution of most prolific authors

Author Name	TP	TC	ACPP	h-index	Affiliated Institution	Country
Dagna, L	19	722	38.00	8	Vita-Salute San Raffaele University	USA
Cavalli, G	15	649	43.27	5	IRCCS San Raffaele Scientific Institute	Italy
Liu, L	14	940	67.14	8	Second Affiliated Hospital of Southern University of Science and Technology	China
Tabarsi, P	13	48	3.69	5	Shahid Beheshti University of Medical Sciences	Iran
Rezaei, N.	12	336	28.00	8	Tehran University of Medical Sciences	Iran
Ascierto, P.A	12	173	14.42	6	Istituto Nazionale Tumori IRCCS - Fondazione G Pascale, Napoli	Italy
Netea, M.G	11	924	84.00	7	Radboud University Nijmegen Medical Centre	Netherlands
Conti, P	11	807	73.36	8	University of G. d'Annunzio Chieti and Pescara	Italy
Fabbrocini, G	11	87	7.91	6	Università degli Studi di Napoli Federico II	Italy
Alharthy, A	10	50	5.00	4	King Saud Hospital Riyadh	Saudi Arabia

Table 2 — Distribution of highly cited documents

Document Title	Authors	TC	Name of Journals	Year
Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China	Huang, C., Wang, Y., Li, X., (...), Wang, J., Cao, B.	15364	The Lancet 395(10223), pp. 497-506	2020
COVID-19: consider cytokine storm syndromes and immunosuppression	Mehta, P., McAuley, D.F., Brown, M., (...), Tattersall, R.S., Manson, J.J.	3320	The Lancet 395(10229), pp. 1033-1034	2020
Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China	Ruan, Q., Yang, K., Wang, W., Jiang, L., Song, J.	1721	Intensive Care Medicine 46(5), pp. 846-848	2020
Dysregulation of immune response in patients with coronavirus 2019 (COVID-19) in Wuhan, China	Qin, C., Zhou, L., Hu, Z., (...), Wang, W., Tian, D.-S.	1461	Clinical Infectious Diseases 71(15), pp. 762-768	2020
Clinical and immunological features of severe and moderate coronavirus disease 2019	Chen, G., Wu, D., Guo, W., (...), Zhao, J., Ning, Q.	1430	Journal of Clinical Investigation 130(5), pp. 2620-2629	2020
Effective treatment of severe COVID-19 patients with tocilizumab	Xu, X., Han, M., Li, T., (...), Pan, A., Wei, H.	997	Proceedings of the National Academy of Sciences of the United States of America 117(20), pp. 10970-10975	2020
Imbalanced Host Response to SARS-CoV-2 Drives Development of COVID-19	Blanco-Melo, D., Nilsson-Payant, B.E., Liu, W.-C., (...), Albrecht, R.A., tenOever, B.R.	893	Cell 181(5), pp. 1036-1045.e9	2020
The pathogenesis and treatment of the 'Cytokine Storm' in COVID-19	Ye, Q., Wang, B., Mao, J.	808	Journal of Infection 80(6), pp. 607-613	2020
Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections	Long, Q.-X., Tang, X.-J., Shi, Q.-L., (...), Chen, J., Huang, A.-L.	791	Nature Medicine 26(8), pp. 1200-1204	2020
Cytokine release syndrome in severe COVID-19: interleukin-6 receptor antagonist tocilizumab may be the key to reduce mortality	Zhang, C., Wu, Z., Li, J.-W., Zhao, H., Wang, G.-Q.	731	International Journal of Antimicrobial Agents 55(5), 105954	2020

With regard to top ten highly cited documents (articles), it is observed from the (Table 2) that article entitled “Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China” received maximum of 15364 total citations, followed by article entitled “COVID-19: consider cytokine storm syndromes and immunosuppression” and “Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China” with total 3320 and 1721 citations, respectively. Five articles received more than 1400+ citations and rest

five articles secured between 700 to 1000 total citations under highly cited document category.

Distribution of most productive journals and highly dynamic organizations

In this study we also evaluated top ten productive journals in the area of concern i.e. interleukins and COVID-19. As demonstrated in the (Table 3), results revealed that “Frontiers in Immunology” has published maximum 161 papers in the domain followed by “Journal of Medical Virology” and “Medical Hypotheses” with 85 and 75 total published

articles in the domain and hence secured top three positions. Study also observed that ranked one and two journals received maximum citations. The journal entitled “Signal Transduction and Targeted Therapy” has minimum 36 publications but secured significant total of 1089 citations and positioned at number three under total citation classification and achieved a top position in average citation per publication. Study also observed that Frontiers Media S.A & Elsevier are the lead publishers in the domain of Interleukins and COVID-19 discipline and “Journal of Medical Virology” received top most h-index.

Table 4 shows the list of organizations contributing the scientific literatures in the discipline of interleukins and COVID-19. Analysis revealed that Tongji Medical College and Huazhong University of Science & Technology contributed maximum i.e. 212 and 210 publications, respectively, and both the institutions received maximum citations.

Analysis also revealed that China and France represented three each institutions followed by two institutes from USA and one from Italy. It is noted that Chinese Academy of Medical Sciences has published minimum 58 papers and has received significant of 17911 total citation and 308.81 average citation per publication.

Analysis of Bibliometric Network Visualizations

The present study has discovered the network visualizations with help of VOSviewer software. Study has explored the relationship of co-authorship with countries, co-occurrence of author keywords, citation analysis with documents, authors and organizations. Study also conducted bibliographic coupling analysis with source titles, countries and documents. All these bibliometric network visualization aspects are important to study in terms of their total network links, clusters and network strength.

Co-authorship analysis when the unit of analysis is Countries

Figure 2 shows the network visualization of co-authorship analysis when unit of analysis is countries. Study set the criteria of minimum of 1 paper from the country with 2 citations of a country. Out of 352 countries, 153 countries met the threshold criteria. Total 24 clusters and 1166 links with total link strength of 3981 were reported in the visualization’s analysis.

Network visualization of Co-occurrence of keywords

The closer of each other keywords in the network visualization map, the stronger is their relevance and interaction with each other to form a cluster (Van Eck

Table 3 — Distribution of highly productive journals

Name of Journals	TP	TC	SJ Rank 20	ACPP	h-index	Publisher
Frontiers In Immunology	161	2420	2.646	15.03	18	Frontiers Media S.A.
Journal Of Medical Virology	85	2304	0.782	27.11	20	Wiley-Blackwell
Medical Hypotheses	75	402	0.441	5.36	11	Elsevier
International Journal of -Infectious Diseases	42	677	1.278	16.12	12	Elsevier
International Journal of -Molecular Sciences	40	423	1.455	10.58	11	MDPI
Frontiers In Pharmacology	40	152	1.384	3.80	7	Frontiers Media S.A
Frontiers In Medicine	39	152	1.388	3.90	8	Frontiers Media S.A
The Lancet Rheumatology	38	1032	1.657	27.16	11	Elsevier
Signal Transduction and -Targeted Therapy	36	1089	4.284	30.25	13	Springer Nature
Critical Care	35	428	2.681	12.23	13	Springer Nature

Table 4 — Distribution of highly dynamic organizations

Affiliations	TP	TC	h- Index	ACPP	Country
Tongji Medical College	212	27001	38	127.36	China
Huazhong University of Science and -Technology	210	26998	37	128.56	China
Inserm	100	3739	24	37.39	France
Harvard Medical School	85	2465	22	29.00	USA
Università degli Studi di Milano	74	1283	21	17.34	Italy
AP-HP Assistance Publique - Hopitaux -de Paris	67	2333	17	34.82	France
Icahn School of Medicine at Mount -Sinai	61	4160	22	68.20	USA
Sapienza Università di Roma	59	882	16	14.95	Italy
Chinese Academy of Medical Sciences & Peking Union Medical College	58	17911	17	308.81	China
Université de Paris	51	2299	18	45.08	France

during the visualization analysis. Study observed that “COVID-19” and “SARS-CoV-2” received maximum occurrences with 2160 and 1109, respectively, and both keywords observed high link strength of 6586 and 3782, respectively.

Conclusion

SARS-CoV-2 infects cells in the lower respiratory system efficiently, leading to a rapid local immunological response. IL-6 levels are significantly elevated in COVID-19 patients and are associated with poor clinical outcomes. Inhibiting IL-6 is thought to be a unique therapeutic strategy for the control of dysregulated host responses in SARS-CoV-2 infection. In view of global mounting public health issue of COVID-19, primarily due to increased viral transmissibility and associated cytokine storm, it will be beneficial for the world at large, to come together and collaborate on further research in the concern area. The present study distillates a comprehensive bibliometric analysis of 4510 scientific research articles published in the preceding three years, indexed in Scopus on emergent area of interleukins and COVID-19. India’s publication on Interleukin has increased year by year exponentially and these publications have appeared in highly reputed journals like Science, Nature, Lancet, Journal of Tumor Biology etc. These publications also received highest citations in comparison to research published in other journals. Hence it can be concluded that Indian publications on interleukin-6 are of high repute. Furthermore, an attempt has been made to describe the relationship of network visualization in terms of clusters, links and total link strength of author, co-authors, citation and bibliographic coupling using VOS viewer tool to comprehend the area of interest.

Nonetheless, a limitation of this analysis should be taken into consideration when interpreting the results for any potential clinical implications. This is the only preliminary investigation to see the trends of research of IL-6 in COVID-19. The present study has only taken Scopus database and not covered the published work in other databases; and for India’s publication in IL-6 Web of science was searched. It would be interesting to examine with large scale including research published and available in Scopus, Web of Science (WoS) and Google Scholars to draw more solid conclusions in this domain. In spite of this limitation, we believe that findings of the study provide enough evidence that will empower researchers from across the spectrum to investigate

the concept and extent of COVID-19, from a global perspective, while facilitating further research in the domain.

Conflict of interest

All authors declare no conflict of interest.

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