

Research trends of Janus Kinase inhibitors: a bibliometric and visualized study from 2012 to 2023

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Abstract. – **OBJECTIVE:** Janus Kinase (JAK) inhibitors have been extensively evaluated for their potential in the management of various diseases. Despite previous research on this topic, there is a lack of bibliometric analysis that summarizes research trends on JAK inhibitors. This study aims to provide a comprehensive overview of the top 100 most frequently cited studies on JAK inhibitors over the last ten years.

MATERIALS AND METHODS: The Web of Science database was used to screen and extract relevant studies on JAK inhibitors. The top 100 studies most cited within the JAK inhibitor-related research were identified and evaluated, and various data such as the year of publication, study focus and keywords, author information, and number of citations were extracted and analyzed for further examination.

RESULTS: In the top 100 most cited studies of JAK inhibitors, more than 70% of studies focused on the role of JAK inhibitors in disease treatments, with 42% of these studies focused on using JAK inhibitors as treatment for autoimmune diseases and 19 of them focused on the treatment of neoplasms. Time trend analysis revealed that the keywords “tofacitinib”, “atopic dermatitis”, and “rheumatoid arthritis” were widely mentioned in 2016, while new trends emerged in 2018, with “ruxolitinib” and “baricitinib” being more commonly mentioned.

CONCLUSIONS: The top 100 most frequently cited studies on JAK inhibitors focused primarily

on the safety and efficacy of these inhibitors in the management of various diseases, particularly inflammatory diseases and neoplasms. The results can serve as a valuable reference for rheumatologists and immunologists interested in the development of JAK inhibitors and expanding future research fields.

Key Words:

Bibliometric analysis, Janus kinase inhibitors, Immunology, Pharmacology, Inflammation.

Introduction

The Janus Kinase/signal transducers and activators of transcription (JAK-STAT) signaling pathway plays a crucial role in regulating numerous cytokines and growth factors involved in various biological processes, such as cell growth, proliferation, the maintenance of internal stability, and immune system regulation¹. In recent years, the use of biologics as a treatment option for inflammatory diseases has generated considerable interest^{2,3}. Janus Kinase (JAK) inhibitors work by targeting the kinase part of JAK proteins, preventing them from phosphorylating and interrupting subsequent intracellular signaling. This mechanism is employed by

first-generation JAK inhibitors, such as ruxolitinib, baricitinib, and tofacitinib, to inhibit various types of JAK. For instance, tofacitinib, approved for psoriatic arthritis by the United States Food and Drug Administration, primarily inhibits JAK-1 and JAK-3, with some specificity for the JAK-2 isoform^{4,5}.

Given the influence of cytokines and cell proliferation, the efficacy and safety of different JAK inhibitors for managing autoimmune diseases and certain neoplasms, such as myelofibrosis, have been widely discussed⁶⁻⁸. Integrated results from randomized controlled trials and real-world evidence have provided valuable insights into the clinical application of JAK inhibitors^{9,10}. However, to date, bibliometric studies providing visual analyses of research trends in the field of JAK inhibitors have been lacking. Therefore, we conducted a bibliometric study with visual analyses based on the top 100 JAK inhibitor studies of the past decade to offer a comprehensive view of the research trends in this field.

Materials and Methods

Searching Strategy

On March 8, 2023, we conducted a search in the Web of Science database, available at <https://www.webofknowledge.com>, using the term “Janus Kinase inhibitor”. Medical Subject Headings (MeSH) terms were employed to identify synonyms. To analyze the research trends of the past decade, we limited the literature to the period from 2012 to 2023. No additional limitations regarding language, publisher, or article types were set. During the screening process, we accessed information from the Web of Science database, such as author names, the number of times an article had been cited, article types, publication dates, research focuses, and open-access status. To ensure consistency and avoid biases resulting from changes in citation updates in the database, we performed all data analyses and extraction on the same day while retrieving data from Web of Science. To gain a better understanding of research trends and developments in the field, we identified the top 100 most cited studies on JAK inhibitors for subsequent bibliometric and visualization analyses. In this study, publications with any of the following criteria were excluded and not subjected to further analysis: (1) studies that did not mention JAK inhibitors; (2) studies focused on the mechanism of the JAK-STAT

signaling pathway but not on JAK inhibitors; (3) unpublished research items. After evaluating the content and research focuses of the studies related to JAK inhibitors, we listed the top 100 most-cited publications. In cases where multiple articles had the same number of citations, priority was given to the article published at a later date and listed first in the sequence.

Data Extraction and Statistical Analysis

We collected and examined data from the 100 publications¹¹⁻¹¹⁰ relevant to JAK inhibitors. This data included details such as article types, main focuses, and citation counts, all of which are presented in **Supplementary Table I**. Publications were categorized based on their main focus. Statistical analysis was conducted using Microsoft Excel 2019 and the Bibliometrix R package software (Naples, Italy), an open-source tool commonly used in previous bibliometric studies across various specialties of clinical medicine^{111,112}. Bibliometrix was utilized to create visualized keyword analyses, including word clouds, co-occurrence analysis, and time-trend analysis, as well as to summarize the basic information of the listed studies¹¹³. In word cloud analysis, keyword frequency was represented by the font size in the word cloud. A greater font size refers to a greater frequency of being mentioned as the keyword in studies. In co-occurrence analysis plots, a thick line in the figure indicates a greater relationship between connected keywords. In time-trend analysis plots, a greater size of the spot represents a greater frequency of being mentioned as keywords.

Results

Publication Time Trend

The time frame for the top 100 most-cited JAK inhibitor studies of the past decade spanned from 2012 to 2021. The year 2017 had the highest number of JAK inhibitor studies listed in the top 100, with 23 studies included^{14,17,21,27,28,31,39,42,45,46,50,54,55,58,59,64,73,76,81,83,84,102,107} (Figure 1). Within the top 100 list of JAK inhibitor studies, the most recent study was a randomized controlled trial by Marconi et al⁴⁰ entitled “Efficacy and safety of baricitinib for the treatment of hospitalized adults with COVID-19 (COV-BARRIER): a phase 3 trial”. This study was published in *The Lancet Respiratory Medicine* in December 2021.

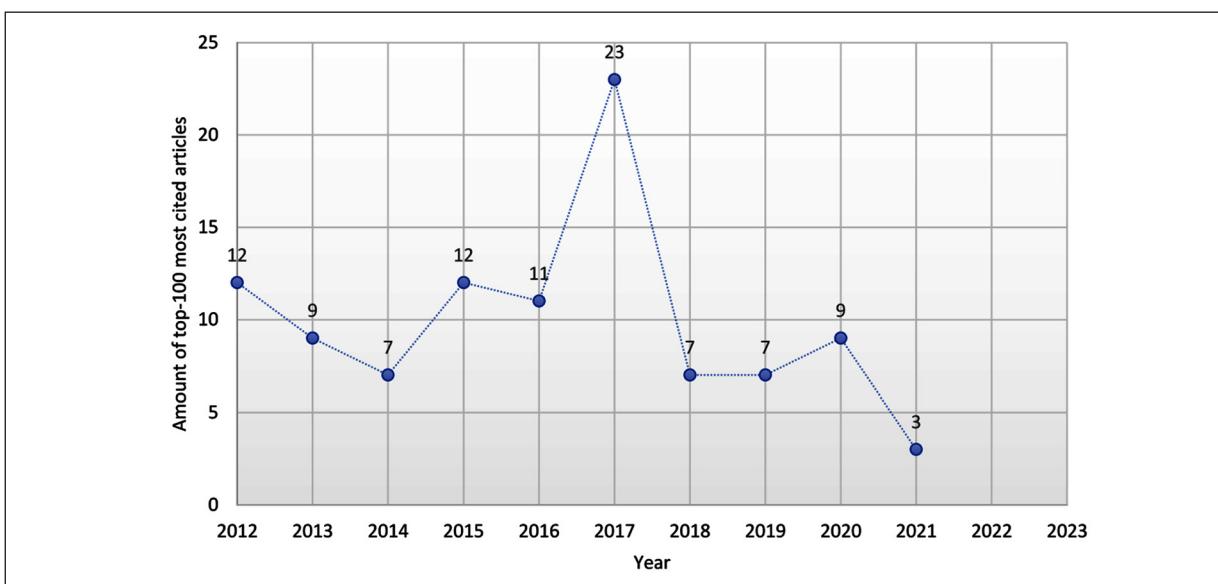


Figure 1. Trend of the most-cited JAK inhibitor studies by year.

Article Types and Cited Times

In the past decade, the top 100 most-cited JAK inhibitor studies have been collectively cited a total of 25,987 times. The number of citation times for individual studies ranged from 135 to 1,358. The highest-cited publication among the top 100 studies was a phase 3 randomized controlled trial¹¹ entitled “A Double-Blind Placebo-Controlled Trial of Ruxolitinib for Myelofibrosis”. This study, conducted by Verstovsek

et al¹¹, evaluated the benefits of ruxolitinib, a selective inhibitor of JAK1/JAK2, in myelofibrosis patients. It was published in the New England Journal of Medicine in March 2012. Among the top 100 JAK inhibitor studies, more than 80% were published as original articles (n=89), with an average of 262.5 citations per article. Review articles comprised 10% of the top 100 JAK inhibitor studies, with an average of 249.1 citations per article (Figure 2).

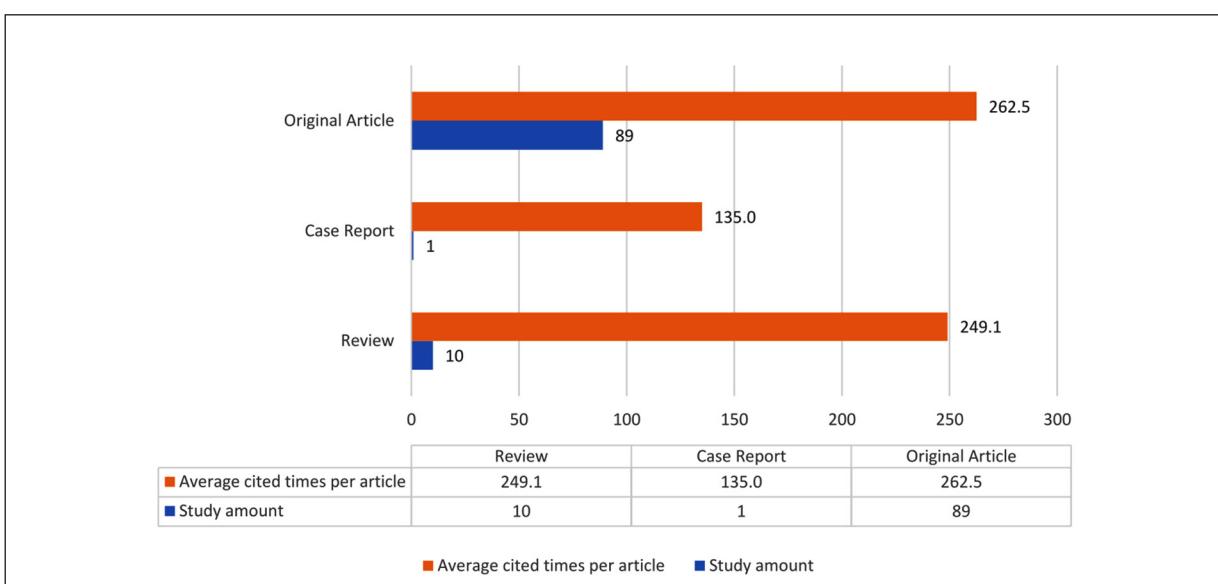


Figure 2. Article type and average cited times per study for the most-cited JAK inhibitor studies.

Publication Details

The publication details are provided in Table I. Among the top-cited JAK inhibitor studies, the New England Journal of Medicine published the most, with 14 articles^{11-19,21,23,27,31,37,60}. Journals that published over 5 of the most-cited articles included The Lancet (n=11)^{20,33,35,39,42,44,52,71,78,94,104}, Annals of Rheumatic Diseases (n=7)^{32,46,54,58,66,73,81}, British Journal of Dermatology (n=6)^{41,48,62,65,88,103}, Arthritis & Rheumatology (n=5)^{45,53,57,93,107}, and Blood (n=5)^{5,36,47,89,91}.

Research Focuses

Figure 3 displays the research focuses of the top 100 list. Among the most-cited JAK inhibitor studies, over 70% (n=77)^{11-16,18-21,23,25-27,29-31,33-42,44-48,50,52,54,56-60,62,71,73-76,78,79,81-85,88,91-96,98-106,109} centered on the role of JAK inhibitors in disease treatments. Specifically, 42 of these studies^{14-16,19-21,23,26,27,29,31,33,35,38,39,41,42,44,45,46-48,52,54,56-59,62,68,71,73,78,79,81,84,88,93,94,98,103} focused on using JAK inhibitors as a treatment for autoimmune diseases, while 19^{11,12,25,30,50,64,67,70,75,76,83,85,91,92,100-102,106,109} addressed the treatment of neoplasms. Notably, five studies in the list mentioned JAK inhibitors as a potential treatment for coronavirus disease 2019 (COVID-19)^{13,40,60,69,105}.

Among studies focusing on the effect of JAK inhibitors on diseases, rheumatoid arthritis (RA) was the most frequently evaluated disease, accounting for 22% of all studies^{15,19-21,23,26,29,38,42,44-47,52,54,56,57,71,73,79,81,93} in the top 100 list. Other specific diseases with more than five studies listed in the top 100 included myelofibrosis (n=15)^{11,12,25,30,50,64,67,70,75,83,85,100,101,102,106}, atopic dermatitis (n=6)^{41,65,82,95,96,104}, psoriasis (n=5)^{35,48,62,88,103}, and inflammatory bowel diseases (n=5)^{14,16,39,59,68}.

Table I. Top 10 journals of the most-cited publications of JAK inhibitors.

Journal names	Amount of studies in the top 100 publications	Impact factor 2021*
New England Journal of Medicine	14	176.082
The Lancet	11	202.731
Annals of the Rheumatic Diseases	7	28.003
British Journal of Dermatology	6	11.113
Arthritis & Rheumatology	5	15.483
Blood	5	25.669
Journal of Allergy and Clinical Immunology	4	14.290
Arthritis & Rheumatism**	3	NA
Journal of Clinical Oncology	3	50.739
Journal of the American Academy of Dermatology	3	15.487

*Impact factor 2021 was retrieved according to the “Journal Citation Report 2021” published by Clarivate. **The journal Arthritis & Rheumatism had been reformed into Arthritis & Rheumatology at 2014; hence IF 2021 was not available.

Keyword Analysis

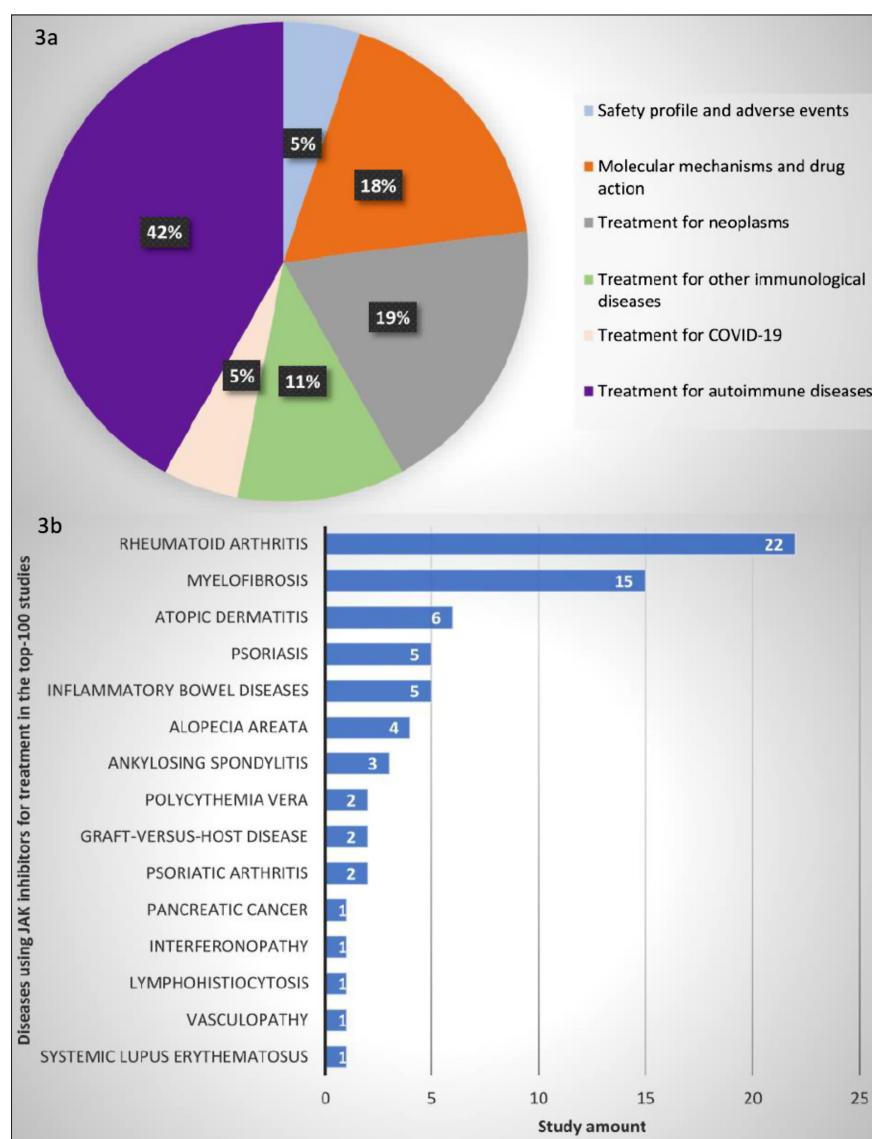
The results of keyword analyses for the most-cited 100 JAK inhibitor studies are presented in Figure 4. In the word cloud analysis, the most frequently mentioned keywords in these studies were “double-blind,” “efficacy,” “safety,” “rheumatoid arthritis,” and “inadequate response”. The co-occurrence analysis examined the interactions and associations among different keywords. The results revealed connections among keywords such as “efficacy,” “safety,” “tofacitinib,” and “rheumatoid arthritis.” Additionally, keywords like “Janus Kinase inhibitor,” “inadequate response,” “methotrexate,” and “modifying antirheumatic drugs” also showed associations. The time-trend analysis demonstrated that in 2016, the keywords “tofacitinib,” “atopic dermatitis,” and “rheumatoid arthritis” were prominently mentioned. However, in 2018, new trends emerged with keywords such as “ruxolitinib” and “baricitinib”. Notably, besides the commonly mentioned keywords “efficacy” and “safety,” the term “COVID-19” became a new trend in JAK inhibitor research in 2020.

Discussion

In this bibliometric study, we visualized the most-cited studies on JAK inhibitors over the past decade. These studies primarily comprised original articles and mainly centered on treating autoimmune diseases and neoplasms. Our study offers a clear insight into the research trends surrounding JAK inhibitors in the last decade.

Among the top 100 most cited JAK inhibitor studies, 22% were related to treating rheumatoid

Figure 3. Summary of topic focuses. **a**, Main focuses of the most-cited JAK inhibitor studies. **b**, Treatment focus of most-cited JAK inhibitor studies, stratified by diseases.



arthritis. According to the 2019 update of the European Alliance of Associations for Rheumatology recommendations for RA management, JAK inhibitors, classified as targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs), have shown comparable efficacy to biologic disease-modifying antirheumatic drugs (bDMARDs). They are considered additional treatment options when conventional synthetic DMARDs (csDMARDs) fail to deliver significant efficacy, especially in patients with poor prognostic factors¹¹⁴. A recent meta-analysis⁹ found that combining JAK inhibitors with methotrexate is more effective in controlling disease activity than JAK inhibitor monotherapy. Currently, several JAK inhibitors, including tofac-

itinib, baricitinib, peficitinib, upadacitinib, and filgotinib, have shown promise as potential options for RA treatment in clinical trials^{44,73,115-117}. According to the results of our study, tofacitinib and baricitinib were two of the most frequently mentioned keywords between 2016 and 2018. Recent research^{44,52,57,71,73,81,93} has also evaluated other JAK inhibitors for RA management. Integrated results from randomized controlled trials¹¹⁸ have demonstrated that peficitinib is non-inferior in controlling disease symptoms when measured using the American College of Rheumatology 20/50/70 criteria. However, variations in selectivity and pharmacodynamic signaling may exist among different JAK inhibitors. Currently, there is a lack of head-to-head

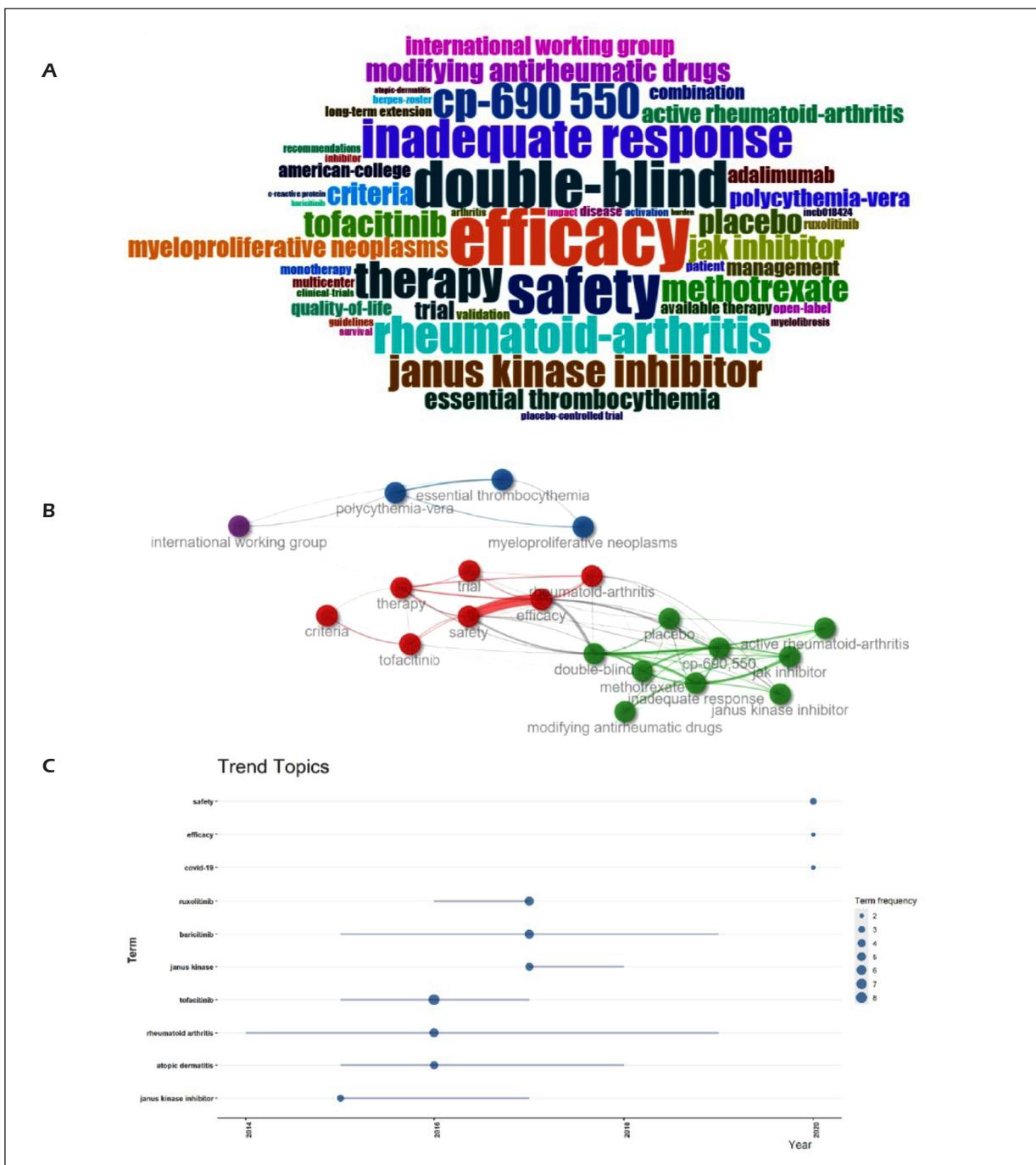


Figure 4. Keyword analysis. **A**, Visualized keyword analysis with word-cloud of most-cited JAK inhibitor studies. **B**, Co-occurrence keyword analysis of most-cited JAK inhibitor studies. **C**, Trend topic keyword analysis of most-cited JAK inhibitor study.

trials to establish the comparative treatment efficacy of different JAK inhibitors with distinct pharmacological mechanisms for RA¹¹⁹. Future studies are needed to assess the comparative efficacy and safety of different JAK inhibitors in managing RA.

In the top 100 studies related to JAK inhibitors, the issue of safety profiles was a major focus of 5% of the listed studies. JAK inhibitors have been reported to increase the risk of future infection, cardiovascular disease, and cancer^{28,120,121}. In a recent meta-analysis¹²², the incidence of herpes

zoster in JAK inhibitors users was of 3.23 per 100 patient-years. However, the difference in herpes zoster risk among different JAK inhibitors was not statistically significant^{122,123}. The evidence regarding some of the adverse events associated with JAK inhibitors remains intriguing. While literature has reported adverse events related to venous thromboembolism, recent real-world studies and meta-analyses¹²⁴⁻¹²⁶ have provided additional insights into this intriguing issue. A population-based cohort study¹²⁷ found a non-significant association between JAK inhibitor use and incident venous thromboembolism in rheumatoid arthritis patients (weighted risk ratio, 1.1; 95% CI, 0.7-1.2). Furthermore, the integrated evidence of randomized controlled trials also supported an insignificant association based on published studies to date^{125,126}. JAK inhibitors were warned to have a potential role in the onset of venous thromboembolism by authorities¹²⁸. Moreover, some studies^{129,130} evaluating adverse events in JAK inhibitor users were retrospective, and like other retrospective pharmacoepidemiologic studies^{131,132}, most could not confirm causation. Larger-scale, longer-term studies are still necessary to determine the risk of venous thromboembolism with JAK inhibitors for different indications.

The results of our bibliometric analysis should be interpreted with caution due to certain limitations in the study design. First, the citation count can only partially reflect research trends. While citation count is widely used in bibliometric studies^{133,134}, it can be influenced by various factors, including journal management policies and external public health events. Therefore, readers should exercise caution and not consider these indicators as direct measures of the absolute impact of specific studies. The primary objective of this analysis was to present trends in citation counts and provide a clear overview of research focusing on JAK inhibitors in the field of clinical immunology and pharmacology.

Conclusions

In summary, over the past decade, JAK inhibitors have been extensively investigated as one of the treatment options for autoimmune diseases and neoplasms. Notably, the treatment of inflammatory diseases such as RA, psoriasis, and atopic dermatitis garnered significant attention among the top 100 JAK inhibitor studies. The findings of this study could be valuable references for rheu-

matologists and immunologists interested in the development of JAK inhibitors and the expansion of future research endeavors.

Conflict of Interest

The authors declare that they have no conflict of interests.

Ethics Approval and Informed Consent

Not applicable.

Authors' Contribution

All the authors involved in drafting or revising the article and approved of the submitted version. Study conception and design: Chang HC, Tsai RY, Lee CY, Kuan YH, Liao WC, Chen SJ and Gau SY. Data acquisition: Chang HC, Chen SJ and Gau SY. Data analysis and demonstration: Chang HC, Tsai RY, Chen SJ and Gau SY. Original draft preparation: Chang HC, Tsai RY, Lee CY, Kuan YH, Liao WC, Chen SJ and Gau SY.

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