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ORIGINAL RESEARCH

# Research Trends of Tyrosine Kinase Inhibitors in EGFR-Mutated Non-Small Cell Lung Cancer: A Bibliometric Analysis

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**Background:** This study seeks to identify research trends and hotspots concerning tyrosine kinase inhibitors (TKIs) for the treatment of epidermal growth factor receptor (EGFR)-mutated non-small cell lung cancer (NSCLC) through a comprehensive bibliometric analysis.

**Methods:** Publications on TKIs and EGFR-mutated NSCLC from 2006 to 2024 were analyzed using VOSviewer, CiteSpace, and R-bibliometrix to visualize collaboration, keyword co-occurrences, and research trends.

**Results:** A total of 962 articles were analyzed, authored by 7,458 researchers from 5,401 institutions across 208 countries. Wu Yi-Long was identified as the most prolific author, contributing 30 publications. AstraZeneca emerged as the industrial leader with 103 articles, while the New England Journal of Medicine was recognized as the primary journal with the highest total link strength. Keyword co-occurrence analysis revealed significant research topics including "gefitinib", "chemotherapy", "open label", and "erlotinib." Moreover, keyword burst analysis indicated notable periods of increased research focus on topics such as "osimertinib" and "liquid biopsy", suggesting emerging trends and current hotspots in the treatment of EGFR-mutated NSCLC.

**Conclusion:** This analysis highlights research trends on TKIs for EGFR-mutated NSCLC, emphasizing the importance of targeted therapies like gefitinib and osimertinib for future research and clinical practice enhancement.

**Keywords:** tyrosine kinase inhibitors, non-small cell lung cancer, bibliometrics, CiteSpace, VOSviewer

## Background

Non-small cell lung cancer (NSCLC) is the predominant form of lung cancer, representing approximately 85% of all lung cancer cases globally.[1] Among the various genetic alterations in NSCLC, mutations in the epidermal growth factor receptor (EGFR) gene are particularly notable These mutations are commonly observed in patients with advanced-stage NSCLC and exhibit significant geographic variability, occurring in approximately 10–15% of Caucasian patients and up to 40% of Asian patients, particularly in East Asian populations.[2] These mutations led to constitutive activation of the EGFR signaling pathway, which drove tumorigenesis by promoting cell proliferation, inhibiting apoptosis, and enhancing metastatic potential.[3] The identification of EGFR mutations has significantly impacted the treatment landscape of NSCLC. Conventional chemotherapy, once the mainstay of treatment, offered limited effectiveness and was frequently accompanied by considerable side effects.[4] However, the discovery of EGFR mutations led to the development of targeted therapies, particularly tyrosine kinase inhibitors (TKIs), which have revolutionized the management of EGFR-mutated NSCLC.[5]

TKIs specifically targeted the tyrosine kinase domain of the EGFR, effectively inhibiting the downstream signaling pathways that drove cancer cell proliferation and survival.[6] In recent years, there has been a significant increase in research focused on TKIs for the treatment of EGFR-mutated NSCLC. First-generation TKIs like gefitinib and erlotinib initially provided targeted therapy options with fewer side effects.[7] However, the inevitable development of resistance,

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often due to the T790M mutation, led to the necessity for more advanced therapeutic options.[8] In response to this challenge, second- and third-generation TKIs, such as afatinib and osimertinib, were developed to specifically target resistance mutations.[9,10] Osimertinib, in particular, has demonstrated remarkable efficacy in both first-line treatment and in cases where resistance to earlier TKIs has developed, making it a cornerstone in the treatment of EGFR-mutated NSCLC.[11] As research on TKIs for EGFR-mutated NSCLC continues to grow, there is an increasing need for comprehensive analysis to explore research trends and current research hotspots.

Bibliometrics is a quantitative analytical method used to examine the vast amount of scientific literature and provided a comprehensive overview of research trends, scientific influence, and the evolution of specific fields over time.[12] By analyzing citation patterns, publication outputs, and collaboration networks, bibliometric studies offer valuable insights into the impact and progression of research areas, identifying key contributors, emerging topics, and gaps in the literature.[13] There have been some bibliometric studies focused on specific areas, such as pharmacogenomics research on TKIs in precision oncology and natural compounds in cancer treatment. Alzoubi et al conducted a bibliometric analysis of pharmacogenomics research on TKIs in precision oncology, highlighting a focus on applied pharmacokinetics and international collaboration, particularly in lung and breast cancer treatment.[14] Yang et al conducted a bibliometric analysis of research on triptolide, highlighting its potential in treating NSCLC through mechanisms like apoptosis induction and gene expression regulation, while also reviewing recent advances in its anti-NSCLC effects and potential in tumor immunotherapy.[15]

To the best of our knowledge, no bibliometric analysis has yet been conducted specifically on TKIs for EGFR-mutated NSCLC. This study aims to conduct a comprehensive bibliometric analysis of research trends on TKIs for EGFR-mutated NSCLC for identifying key research trends and future directions in this rapidly evolving field.

# Methods

## Search Strategies and Data Collection

A literature search was performed using the Web of Science Core Collection (WoSCC)[16] to explore TKIs for the treatment of EGFR-mutated NSCLC from January 1, 2006, to June 30, 2024. To ensure clarity regarding the inclusion of 2024 data, we conducted the final literature retrieval on July 29, 2024, using a predefined search strategy. Given that 2024 was still ongoing at the time of data collection, only articles published up to June 30, 2024, were included in the analysis. The search formula was composed of EGFR, NSCLC, and TKI-related keywords, with the full details available in the Supplementary File 1. [17–19] Only English-language publications were included, focusing solely on articles among the various document types. To avoid discrepancies from database updates, bibliographic information was exported using the "Full record and cited references" and "plain text" formats. Data were collected in text format, encompassing publication and citation counts, titles, author details, institutions, countries/regions, keywords, and journals for subsequent bibliometric analysis.

The literature retrieval process was performed by two independent reviewers. Subsequently, both reviewers independently screened the titles and abstracts to identify eligible studies according to the predefined inclusion criteria. Any discrepancies in the selection of articles were resolved through discussion, and in cases where consensus could not be reached, the final decision was made by a third senior reviewer.

## Statistical Analysis

In this research, we selected appropriate software tools to analyze different aspects of the dataset for optimal presentation. VOSviewer (version 1.6.20), CiteSpace (version 6.1.R2), and the R-bibliometrix package (version 3.2.1) were chosen due to their established effectiveness in bibliometric visualization and trend analysis. VOSviewer played a pivotal role in visually mapping institutional and author collaborations, as well as elucidating patterns of co-authorship and citation.[20] In the present study, VOSviewer primarily conducted the following analyses: country and institution analysis, journal and co-cited journal analysis, author and co-cited author analysis, and keyword co-occurrence analysis. In the maps generated by VOSviewer, node size represents the number of publications associated with a particular keyword, author, or institution. Node color denotes different clusters or time periods, enabling the differentiation of various

research areas or time frames. Line thickness between nodes signifies the strength of connections, such as co-authorships or citation links, with thicker lines indicating stronger or more frequent connections.

CiteSpace was employed primarily to detect research frontiers through keyword burst analysis. The parameters were configured as follows: time slicing was conducted from January 2006 to July 2024, with keywords designated as the node type. The selection of parameter values was based on previous bibliometric study and methodological standards in the field.[21] The rest was set to the specific value, and the cutting method can be set as necessary in accordance with the selected nodes, such that the result would be the most stable, transparent, and intuitive. Visualization analysis was performed based on these parameters to generate a timeline of keywords associated with TKIs for treating EGFR-mutated NSCLC.

The online R package "bibliometrix" (https://www.bibliometrix.org) facilitated comprehensive citation analysis and H-index calculations. The H-index was used to quantify the academic impact of both individuals and journals, offering a balanced measure of academic influence.[22,23] Journal Citation Reports (JCR) quartiles and Impact Factor (IF) were employed to assess the prestige and citation influence of journals. JCR quartiles categorize journals into four tiers, with Q1 representing the highest level of academic impact, while the IF quantifies the average number of citations received by articles published in a journal over the previous two years. For this analysis, we employed the most recent 2024 release of JCR and IF data to ensure an up-to-date assessment of journal prestige and citation influence. Additionally, Microsoft Office Excel 2019 was used to conduct quantitative analysis of publication.

# Results

## An Overview of Publications

Initially, 1,341 studies were identified from the WoSCC. After screening, 379 records were excluded based on predefined criteria to ensure relevance and quality. Specifically, eight non-English articles were excluded to maintain consistency in language. Additionally, 192 review articles, 122 meeting abstracts, 33 editorial materials, 15 early access publications, four letters, three corrections, two retracted publications, and one publication with an expression of concern were removed (Figure 1). Finally, a total of 962 articles were included in the final analysis, which were contributed by 7,458 authors from 5,401 institutions across 208 countries/regions, published in 239 journals and cited 16,508 references. As shown in Figure 2, the total number of publications related to research on TKIs for EGFR-mutated NSCLC has steadily increased over the years, beginning with a single publication in 2006. The field began to gain momentum around 2012, with a noticeable rise in the number of articles published each year. From 2016 to 2023, there was a substantial linear increase in publications, reflecting growing interest and advancements in this area of study. Notably, even though 2024 is not yet complete, it has already seen 64 publications, indicating that the upward trend is likely to continue.

The most frequently cited article, titled "Osimertinib in Untreated EGFR-Mutated Advanced Non–Small-Cell Lung Cancer", was published in 2018, which has an IF of 96.2, and has accumulated a total of 3,156 citations.[24] The second most cited article, "AZD9291 in EGFR Inhibitor–Resistant Non–Small-Cell Lung Cancer", was published in 2015 and has garnered 1,674 citations.[25] The third most cited article, "Overall Survival with Osimertinib in Untreated, EGFR-Mutated Advanced NSCLC", published in 2020, has received 1,566 citations to date.[11] All three of these highly cited articles were published in the *New England Journal of Medicine*.

## Analysis of the Countries

As shown in Figure 3A (generated by R-bibliometrix) and Table 1, the top 20 most productive countries generated 930 articles. China led the field with 349 publications, accounting for the highest total publications (TP=1,701) and ranking second in total citations (TC=6,730), with an average of 19.3 citations per publication. Japan followed with 163 articles, ranking second in total publications (TP=1,178) and third in total citations (TC=4,325), with an average citation rate of 26.5, underscoring its substantial contribution to the field. The USA, with 98 articles, ranked third in total publications but led in total citations (TC=11,532), resulting in an impressive average of 117.7 citations per publication. Italy also made a strong contribution with 69 articles, ranking fourth in both total publications (TP=500) and total citations (TC=2,203), with an average of 31.9 citations per publication. Notably, the ratio of multiple country

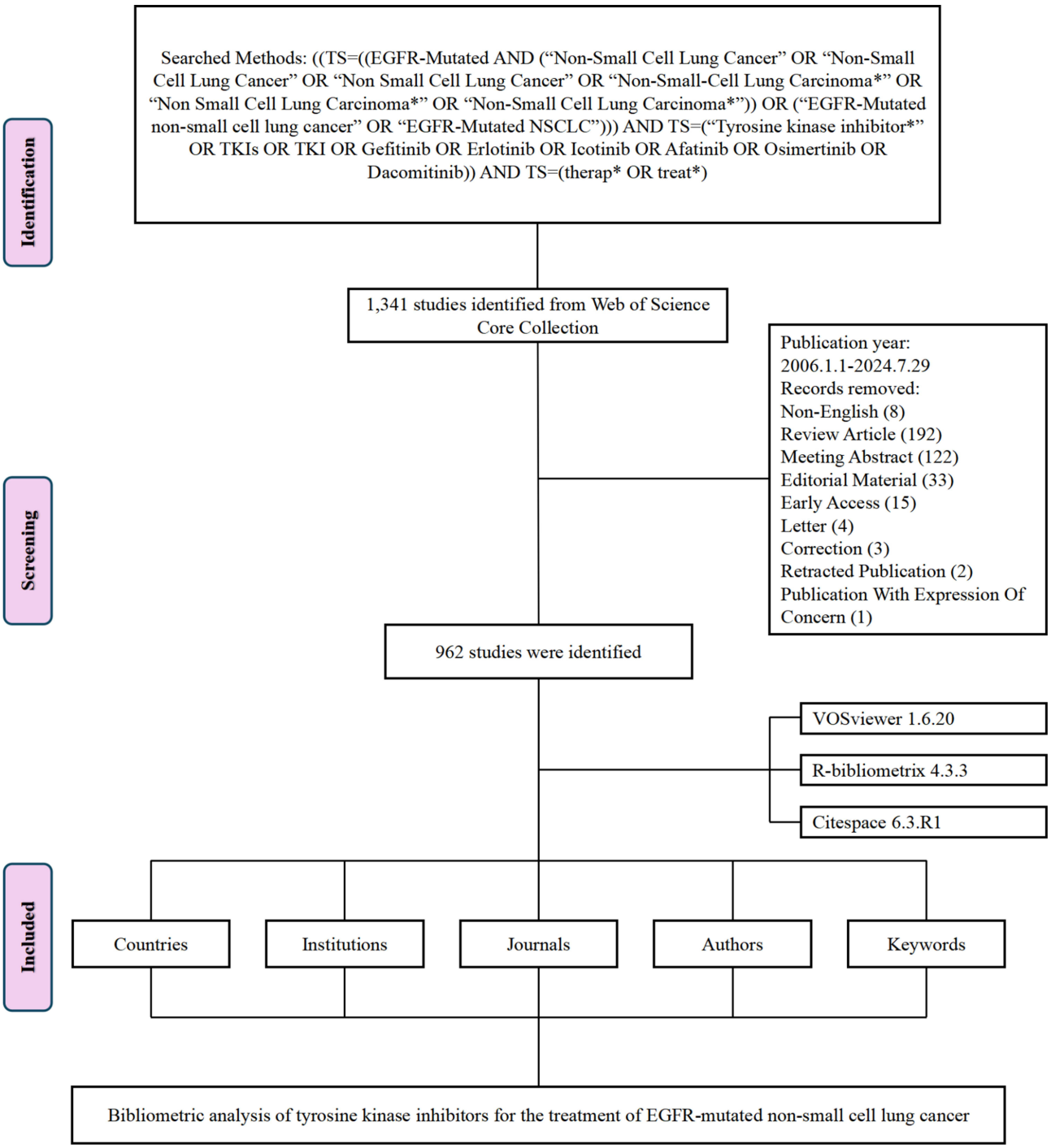


**Figure 1** Flowchart of the literature screening process.

publications (MCP) to single country publications (SCP) varied among these countries, reflecting different levels of international collaboration. For example, the USA had a high MCP ratio of 0.388, indicating significant international collaboration, while China, despite its large volume of publications, had a lower MCP ratio of 0.138, suggesting more domestically focused research efforts (Figure 3A and Table 1).

The visualization map illustrating the collaboration among different countries in the research on TKIs for EGFR-mutated NSCLC is presented in Figure 3B (generated by VOSviewer). Among the 43 countries involved in international collaborations with a minimum of 2 articles, the USA exhibited a strong collaborative network, as indicated by its high

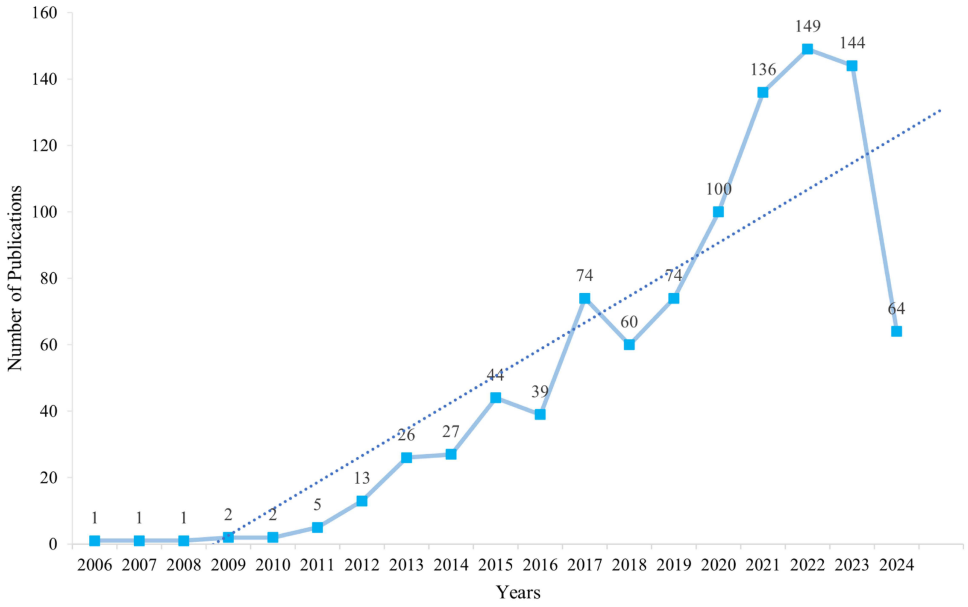


**Figure 2** Overview of publications in research.

total link strength of 413 and significant citation count of 16,305. China also showed substantial collaborative efforts, with a total of 17,177 citations and a total link strength of 355. Japan displayed considerable collaboration strength with a total link strength of 311.

## Analysis of Institutions and Companies

The top ten institutions based on article count and rank in the field are shown in Figure 4A (generated by R-bibliometrix). AstraZeneca stood out as an industrial leader with 103 articles, reflecting its leading role in research and development in this field. UNICANCER closely followed with 102 articles, showcasing its significant contributions to advancing knowledge in this area. Among academic institutions, the National Taiwan University was notable with 76 articles, underscoring its influence and active involvement in the research community. Supporting this data, AstraZeneca also led in citation impact, with 36 documents amassing 9,713 citations. The National Cancer Center and Yonsei University were also prominent, with 37 and 25 documents garnering 7,240 and 6,022 citations, respectively.

The visualization map illustrated the collaboration among 114 institutions involved in research on TKIs for EGFR-mutated NSCLC (Figure 4B, generated by VOSviewer). AstraZeneca stood out with the highest total link strength of 232, highlighting its extensive collaborative network within this research area. The National Taiwan University Hospital followed with a total link strength of 175, demonstrating its significant role in international research collaborations. The National Cancer Center, with a total link strength of 153, and the National Taiwan University, with 149, were also key players, indicating strong partnerships in this field.

## Analysis of Authors

The top 20 productive authors in the field of TKIs for EGFR-mutated NSCLC are listed in Table 2. Wu Yi-Long led the group with 30 publications, reflecting high productivity with an h-index of 17 and a total citation count of 2,451. Tiseo M. followed closely with 28 publications, an H-index of 17, and a total of 6,830 citations, showcasing significant influence in the field. Cho BC also stood out with 25 publications, an H-index of 18, and a remarkable total citation count of 10,797, placing him third in citation ranking, underscoring his substantial impact on the research community. Other notable contributors included Nakagawa K, with 27 publications and an H-index of 15, and Kim SW, with 23 publications and an H-index of 12, both of whom have made significant contributions to the advancement of this research area. Figure 5 (generated by VOSviewer) illustrated the collaboration among various authors. Wu Yi-Long leads with the highest total link strength of 186, indicating


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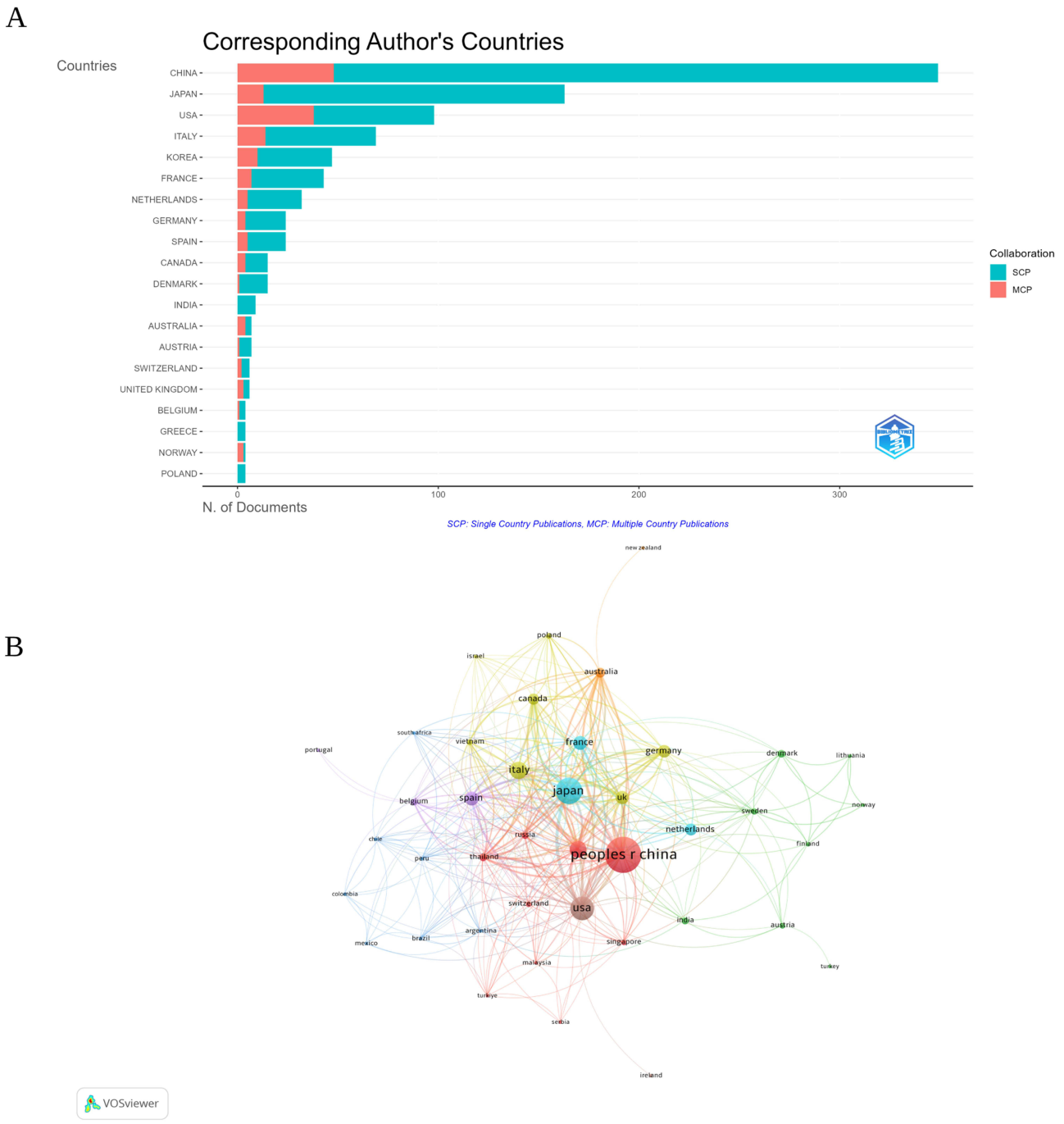


**Figure 3** (**A**) Distribution of corresponding author's publications by country. SCP: Single Country Publications. MCP: Multiple Country Publications. (**B**) Visualization map depicting the collaboration among different countries.

a strong and extensive network of collaborations. Kim SW follows with a total link strength of 156, reflecting significant collaborative efforts. Frances A. Shepherd and Kato Terufumi also showed substantial collaboration, with total link strengths of 140 and 135, respectively.

## Analysis of Journals

A detailed overview of the top 20 most productive journals is shown in Table 3. *Lung Cancer* emerged as the leading journal with an H-index of 30, an IF of 4.5, and a total of 88 publications, ranking first in TP and sixth in total citations

**Table 1** Publication and Citation Profiles of Leading Countries

| Country | Articles | Freq | SCP | MCP | MCP_Ratio | TP | TP_Rank | TC | TC_Rank | Average Citations |
|---|---|---|---|---|---|---|---|---|---|---|
| CHINA | 349 | 0.363 | 301 | 48 | 0.138 | 1701 | 1 | 6730 | 2 | 19.3 |
| JAPAN | 163 | 0.169 | 150 | 13 | 0.080 | 1178 | 2 | 4325 | 3 | 26.5 |
| USA | 98 | 0.102 | 60 | 38 | 0.388 | 581 | 3 | 11.532 | 1 | 117.7 |
| ITALY | 69 | 0.072 | 55 | 14 | 0.203 | 500 | 4 | 2203 | 4 | 31.9 |
| SOUTH KOREA | 47 | 0.049 | 37 | 10 | 0.213 | 360 | 6 | 2065 | 5 | 43.9 |
| FRANCE | 43 | 0.045 | 36 | 7 | 0.163 | 425 | 5 | 1253 | 6 | 29.1 |
| NETHERLANDS | 32 | 0.033 | 27 | 5 | 0.156 | 169 | 9 | 881 | 8 | 27.5 |
| GERMANY | 24 | 0.025 | 20 | 4 | 0.167 | 211 | 8 | 652 | 9 | 27.2 |
| SPAIN | 24 | 0.025 | 19 | 5 | 0.208 | 225 | 7 | 403 | 11 | 16.8 |
| CANADA | 15 | 0.016 | 11 | 4 | 0.267 | 125 | 10 | 361 | 12 | 24.1 |
| DENMARK | 15 | 0.016 | 14 | 1 | 0.067 | 55 | 14 | 319 | 14 | 21.3 |
| INDIA | 9 | 0.009 | 9 | 0 | 0.000 | 36 | 18 | 321 | 13 | 35.7 |
| AUSTRALIA | 7 | 0.007 | 3 | 4 | 0.571 | 79 | 12 | 954 | 7 | 136.3 |
| AUSTRIA | 7 | 0.007 | 6 | 1 | 0.143 | 38 | 16 | 145 | 15 | 20.7 |
| SWITZERLAND | 6 | 0.006 | 4 | 2 | 0.333 | 42 | 15 | 41 | 22 | 6.8 |
| UK | 6 | 0.006 | 3 | 3 | 0.500 | 100 | 11 | 110 | 16 | 18.3 |
| BELGIUM | 4 | 0.004 | 3 | 1 | 0.250 | 29 | 20 | 497 | 10 | 124.2 |
| GREECE | 4 | 0.004 | 4 | 0 | 0.000 | 65 | 13 | 18 | 26 | 4.5 |
| NORWAY | 4 | 0.004 | 1 | 3 | 0.750 | 26 | 22 | 55 | 17 | 13.8 |
| POLAND | 4 | 0.004 | 4 | 0 | 0.000 | 24 | 24 | 40 | 23 | 10 |

**Abbreviations**: Publications of Corresponding Authors only. Freq, Frequency of Total Publications; MCP_Ratio, Proportion of Multiple Country Publications; TP, Total Publications; TP_rank, Rank of Total Publications; TC, Total Citations; TC_rank, Rank of Total Citations; Average Citations, The average number of citations per publication.

(TC=1,342). The relatively lower citation impact of Lung Cancer may be attributed to the fact that it publishes a high volume of articles, some of which might be less frequently cited. *Journal of Thoracic Oncology* held the second position in TP with 36 publications and ranked third in total citations (TC=2,134), underscoring its significant impact in the field. *Clinical Lung Cancer* ranked third in total publications (TP=45) but had a more modest citation impact, ranking 12th in total citations (TC=377). Notably, *Journal of Clinical Oncology*, despite ranking 12th in TP with 16 publications, achieves the highest total citation count (TC=2,457), reflecting its substantial influence and prominence within the research community. This may be attributed to the fact that articles published in this journal tend to be highly influential and frequently cited in clinical and translational research.

The journals featured in the research co-occurrence network diagram related to the field of TKIs for the treatment of EGFR-mutated NSCLC are depicted in Figure 6A (generated by VOSviewer). The three key journals with the highest total link strength in these co-occurrence networks were the *New England Journal of Medicine* with a total link strength of 525, *Lung Cancer* with a total link strength of 318, and the *Journal of Clinical Oncology* with a total link strength of 232. The coupling network diagram of journals is presented in Figure 6B (generated by VOSviewer). The three key journals with the highest total link strength in this coupling network are *Lung Cancer* with a total link strength of 59,059, *Clinical Lung Cancer* with a total link strength of 30,571, and *BMC Cancer* with a total link strength of 24,950.

## Analysis of the Keywords

Figure 7 (generated by VOSviewer) depicted the keyword co-occurrence network in the study of TKIs and EGFR-mutated NSCLC. The keyword co-occurrence analysis clusters the research into two main themes. First, drug-specific research is emphasized by keywords like "gefitinib" (365 occurrences, total link strength of 2,131), "erlotinib" (255 occurrences, total link strength of 1,635), and "osimertinib" (141 occurrences, total link strength of 704). The second theme focuses on treatment strategies, with keywords such as "open-label" (293 occurrences, total link strength of 1,873), "chemotherapy" (303 occurrences, total link strength of 1,866), "1st-line treatment" (199 occurrences, total link

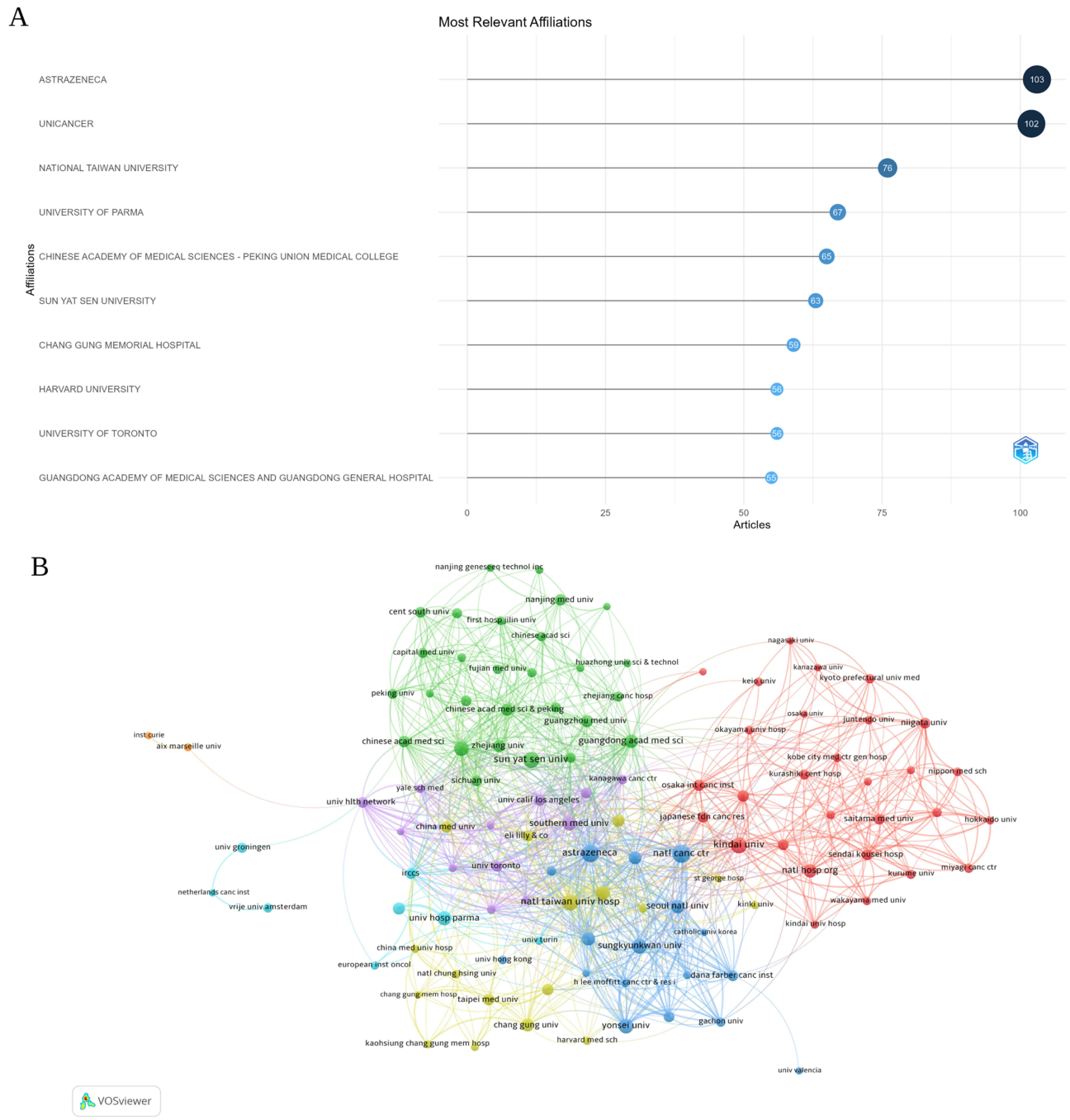


**Figure 4** (**A**) Top ten institutions by article count and rank. Circle size shows article count. Darker shades indicate higher ranks. (**B**) Visualization map depicting the collaboration among different institutions.

strength of 1,302), and "mutations" (188 occurrences, total link strength of 998), emphasizing the significance of therapy sequencing and genetic profiling (Supplemental Table 1).

## Analysis of Burst Keywords

A burst analysis of keywords from 2006 to 2024 revealed the evolution of research trends on TKIs for the treatment of EGFR-mutated NSCLC (Figure 8, generated by CiteSpace). "Growth factor receptor" experienced a significant citation burst from 2007 to 2016, indicating a sustained research interest during that period. Similarly, "gene mutations" and "activating mutations" showed notable bursts from 2009 to 2017 and 2010 to 2016, respectively, underscoring their

**Table 2** Publication and Citation Profiles of High-Impact Authors

| Authors | h_Index | g-Index | m-Index | PY_Start | TP | TP_Frac | TP_Rank | TC | TC_Rank |
|---|---|---|---|---|---|---|---|---|---|
| CHO BC | 18 | 25 | 1.636 | 2014 | 25 | 1.60 | 4 | 10,797 | 3 |
| YANG JCH | 18 | 23 | 1.800 | 2015 | 23 | 1.46 | 6 | 5105 | 9 |
| TISEO M | 17 | 28 | 1.417 | 2013 | 28 | 1.85 | 2 | 6830 | 8 |
| WU YL | 17 | 30 | 1.700 | 2015 | 30 | 2.47 | 1 | 2451 | 14 |
| NAKAGAWA K | 15 | 27 | 1.154 | 2012 | 27 | 2.36 | 3 | 1695 | 17 |
| CHENG Y | 14 | 20 | 2.000 | 2018 | 20 | 1.13 | 8 | 10,059 | 4 |
| AHN MJ | 13 | 21 | 1.300 | 2015 | 21 | 1.69 | 7 | 2573 | 12 |
| JOHN T | 13 | 17 | 1.300 | 2015 | 17 | 0.81 | 15 | 8249 | 6 |
| KIM DW | 12 | 18 | 0.923 | 2012 | 18 | 1.08 | 10 | 3798 | 11 |
| KIM SW | 12 | 23 | 1.200 | 2015 | 23 | 1.30 | 5 | 4353 | 10 |
| LEE KH | 12 | 17 | 1.333 | 2016 | 17 | 0.68 | 16 | 11.150 | 2 |
| PLANCHARD D | 12 | 13 | 1.200 | 2015 | 13 | 0.81 | 35 | 11.366 | 1 |
| RAMALINGAM SS | 12 | 14 | 1.200 | 2015 | 14 | 0.84 | 30 | 7682 | 7 |
| SMIT EF | 12 | 16 | 1.000 | 2013 | 16 | 2.09 | 20 | 667 | 20 |
| HAYASHI H | 11 | 19 | 1.100 | 2015 | 19 | 1.46 | 9 | 689 | 19 |
| LU S | 11 | 18 | 1.222 | 2016 | 18 | 1.03 | 11 | 2568 | 13 |
| OKAMOTO I | 11 | 15 | 0.846 | 2012 | 15 | 0.93 | 24 | 8737 | 5 |
| DE MARINIS F | 10 | 14 | 1.111 | 2016 | 14 | 0.91 | 27 | 1438 | 18 |
| GOLDMAN JW | 10 | 12 | 1.000 | 2015 | 12 | 0.69 | 38 | 2117 | 16 |
| KIM JH | 10 | 13 | 0.833 | 2013 | 13 | 1.06 | 32 | 2254 | 15 |

**Abbreviations**: H_index, The h-index of the journal; which measures both the productivity and citation impact of the publications. g_index, The g-index of the journal, which gives more weight to highly cited articles; m_index, The m-index of the journal, which is the h-index divided by the number of years since the first published paper; TP, Total Publications; TP_rank, Rank of Total Publications; TC, Total Citations; TC_rank, Rank of Total Citations. Average Citations, The average number of citations per publication; PY_start, Publication Year Start, indicating the year the journal started publication.

importance in early research on EGFR-mutated lung cancer. More recent keywords such as "osimertinib" and "liquid biopsy" have exhibited strong bursts from 2019 to 2024 and 2020 to 2022, respectively, suggesting these are current areas of active research and significant contributions to the literature. The keyword "mechanisms" has shown a burst from 2021 and is ongoing, reflecting an emerging interest in understanding the underlying processes involved in drug resistance and treatment efficacy.

# Discussion

## General Information

This bibliometric analysis provides a comprehensive overview of research trends on TKIs for the treatment of EGFR-mutated NSCLC. By analyzing 962 publications from 2006 to mid-2024, the study identifies key contributors, influential publications, and emerging research trends. Patterns in publication trends, geographic contributions, and institutional influence align with the study's objectives. Notably, the distribution of the 32 publications outside the top 20 nations was attributed to smaller contributions from countries not listed in the top 20, demonstrating the broad international scope of TKI research.

Some inconsistencies in citation metrics were observed. For example, the 2020 paper titled "Overall Survival with Osimertinib" had a high citation count (1,566) due to its immediate clinical relevance, publication in a high-impact journal, and frequent referencing in subsequent studies, underscoring its transformative impact on clinical practice.[11] Similarly, the 2018 article in the *New England Journal of Medicine*, with an IF of 96.2 in 2023, reflects the journal's overall prestige rather than the specific article's impact.[24] The variation in journal citation metrics highlights differences in influence. For instance, the *Journal of Clinical Oncology*, ranked 12th in total publications, is first in citations, reflecting the high impact of select articles. In contrast, *Lung Cancer*, ranked first in total publications, is sixth in citations, signifying a broader but less concentrated impact. These patterns emphasize the importance of evaluating both publication volume and citation influence to understand journal contributions.

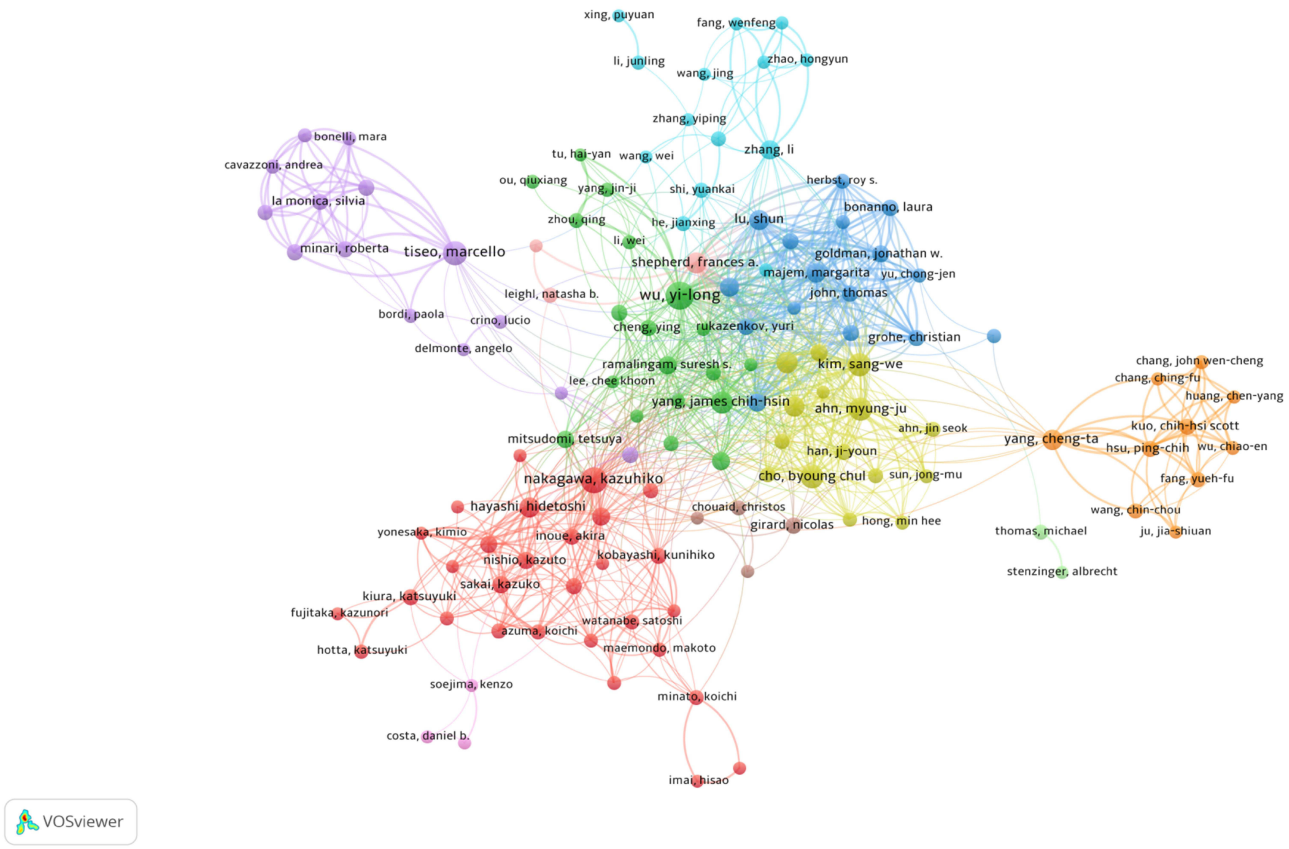


**Figure 5** Visualization map depicting the collaboration among different authors.

China, Japan, and the USA emerged as major contributors to TKI research. Lung cancer is the leading cause of cancer-related deaths in China, with 2015 data estimating 733,000 new cases and 610,000 deaths, which accounted for 17% of total cancer incidence, and 610,000 lung cancer deaths, accounting for 21.7% of total cancer mortality.[26] This high disease burden likely drives China's substantial research output, reflected in its 349 independent publications and a TP of 1,701, including international collaborations. The USA, despite being ranked third in publications, leads in total citations, highlighting the importance of international collaboration (evidenced by its high MCP ratio). In contrast, China's lower MCP ratio reflects a primary focus on domestic research. This distinction underscores China's dual role in advancing independent research and contributing to global collaborations, a factor that merits greater recognition.

**Table 3** Top 20 Most Productive Journals in the Field of Tyrosine Kinase Inhibitors for the Treatment of EGFR-Mutated Non-Small Cell Lung Cancer

| Journal | H_Index | IF 2023 | JCR 2023 | TP | TP_Rank | TC | TC_Rank | PY_Start |
|---|---|---|---|---|---|---|---|---|
| LUNG CANCER | 30 | 4.5 | 1 | 88 | 1 | 1342 | 6 | 2012 |
| JOURNAL OF THORACIC ONCOLOGY | 28 | 21.0 | 1 | 36 | 3 | 2134 | 3 | 2006 |
| CLINICAL LUNG CANCER | 15 | 3.3 | 2 | 45 | 2 | 377 | 12 | 2011 |
| ONCOTARGET | 15 | / | / | 18 | 9 | 525 | 9 | 2014 |
| CLINICAL CANCER RESEARCH | 15 | 10.0 | 1 | 17 | 10 | 1566 | 5 | 2011 |
| BMC CANCER | 11 | 3.4 | 2 | 35 | 4 | 225 | 24 | 2015 |
| JOURNAL OF CLINICAL ONCOLOGY | 12 | 42.1 | 1 | 16 | 12 | 2457 | 1 | 2011 |
| TARGETED ONCOLOGY | 9 | 4.4 | 2 | 16 | 13 | 103 | 51 | 2015 |
| THORACIC CANCER | 9 | 2.3 | 2 | 34 | 5 | 147 | 41 | 2016 |
| TRANSLATIONAL LUNG CANCER RESEARCH | 9 | 4.0 | 1 | 23 | 8 | 229 | 23 | 2019 |

(*Continued*)

**Table 3** (Continued).

| Journal | H_Index | IF 2023 | JCR 2023 | TP | TP_Rank | TC | TC_Rank | PY_Start |
|---|---|---|---|---|---|---|---|---|
| CANCERS | 7 | 4.5 | 1 | 26 | 7 | 191 | 31 | 2019 |
| CANCER CHEMOTHERAPY AND PHARMACOLOGY | 7 | 2.7 | 2 | 11 | 17 | 170 | 38 | 2015 |
| ANTICANCER RESEARCH | 6 | 1.6 | 4 | 12 | 15 | 131 | 45 | 2010 |
| FUTURE ONCOLOGY | 6 | 3.0 | 2 | 17 | 11 | 138 | 42 | 2014 |
| CANCER SCIENCE | 8 | 4.5 | 1 | 10 | 19 | 174 | 35 | 2008 |
| ONCOTARGETS AND THERAPY | 7 | 2.7 | 3 | 14 | 14 | 173 | 37 | 2013 |
| PLOS ONE | 7 | 2.9 | 1 | 10 | 21 | 405 | 10 | 2013 |
| EUROPEAN JOURNAL OF CANCER | 6 | 7.6 | 1 | 10 | 20 | 298 | 15 | 2020 |
| INTERNATIONAL JOURNAL OF MOLECULAR SCIENCES | 5 | 4.9 | 2 | 12 | 16 | 87 | 56 | 2020 |
| CANCER MEDICINE | 4 | 2.9 | 2 | 11 | 18 | 62 | 69 | 2019 |

**Abbreviations**: H_index, The h-index of the journal, which measures both the productivity and citation impact of the publications; IF, Impact Factor, indicating the average number of citations to recent articles published in the journal; JCR_Quartile, The quartile ranking of the journal in the Journal Citation Reports, indicating the journal's ranking relative to others in the same field (Q1: top 25%, Q2: 25%-50%, Q3: 50%-75%, Q4: bottom 25%); TP, Total Publications; TP_rank, Rank of Total Publications; TC, Total Citations; TC_rank, Rank of Total Citations. Average Citations; The average number of citations per publication.PY_start, Publication Year Start, indicating the year the journal started publication.

Institutional analysis identified AstraZeneca and the National Taiwan University as leading contributors. AstraZeneca, a prominent pharmaceutical company, has been instrumental in developing EGFR-targeted TKIs, such as ZD-1839 (gefitinib), aimed at treating NSCLC patients with EGFR overexpression.[27] However, AstraZeneca's citation impact (9,713 citations across 36 papers) appears inconsistent with its TP count of 103 articles, reflecting a methodological distinction between citation analysis and overall output.

Prominent authors such as Wu Yi-Long and Cho BC were identified as key contributors. Wu Yi-Long's research demonstrated that EGFR mutations, particularly in non-smokers and adenocarcinoma patients, significantly improve responses to TKIs like gefitinib, shaping clinical guidelines for EGFR-targeted therapies.[28] Interestingly, Wu Yi-Long's higher publication count but lower H-index compared to Cho BC highlights differences in their long-term impact versus research volume, illustrating the nuanced relationship between productivity and influence.

## Research Hotspots

The keyword co-occurrence analysis of TKIs research for EGFR-mutated NSCLC can be clustered into two main themes. First, drug-specific research, with keywords like "gefitinib", "erlotinib", and "osimertinib", underscores the central role these drugs play in treatment. Both gefitinib and erlotinib are first-generation TKIs that have significantly changed the treatment landscape for NSCLC.[29] Osimertinib is a third-generation TKI that was initially developed to target the T790M resistance mutation, which is a common cause of resistance to first-generation TKIs like gefitinib and erlotinib. Osimertinib has shown superior efficacy in the first-line setting, particularly in prolonging overall survival compared to gefitinib and erlotinib.[30] Second, treatment strategies are highlighted by keywords such as "chemotherapy", "1st-line treatment", "open label", and "mutations", emphasizing the importance of therapy sequencing and genetic profiling. The choice of 1st-line treatment for NSCLC is increasingly influenced by the presence of genetic mutations. Patients with activating EGFR mutations are often treated with EGFR-TKIs as a first-line option, which has been shown to improve progression-free survival compared to traditional chemotherapy.[31] Key terms such as "open label". which emerged as significant in keyword analyses, signify the prevalence of open-label clinical trials in TKI research. These studies have been instrumental in evaluating the safety and efficacy of EGFR-TKIs, often forming the basis for regulatory approvals and clinical guidelines.

## Research Frontiers

The keyword "growth factor receptor" experienced a significant burst of citations in 2007–2016. This reflects the initial focus on understanding the role of growth factor receptors, particularly EGFR, in the pathogenesis of NSCLC. The importance of this keyword during this period aligns with the development of first-generation EGFR TKIs, such as

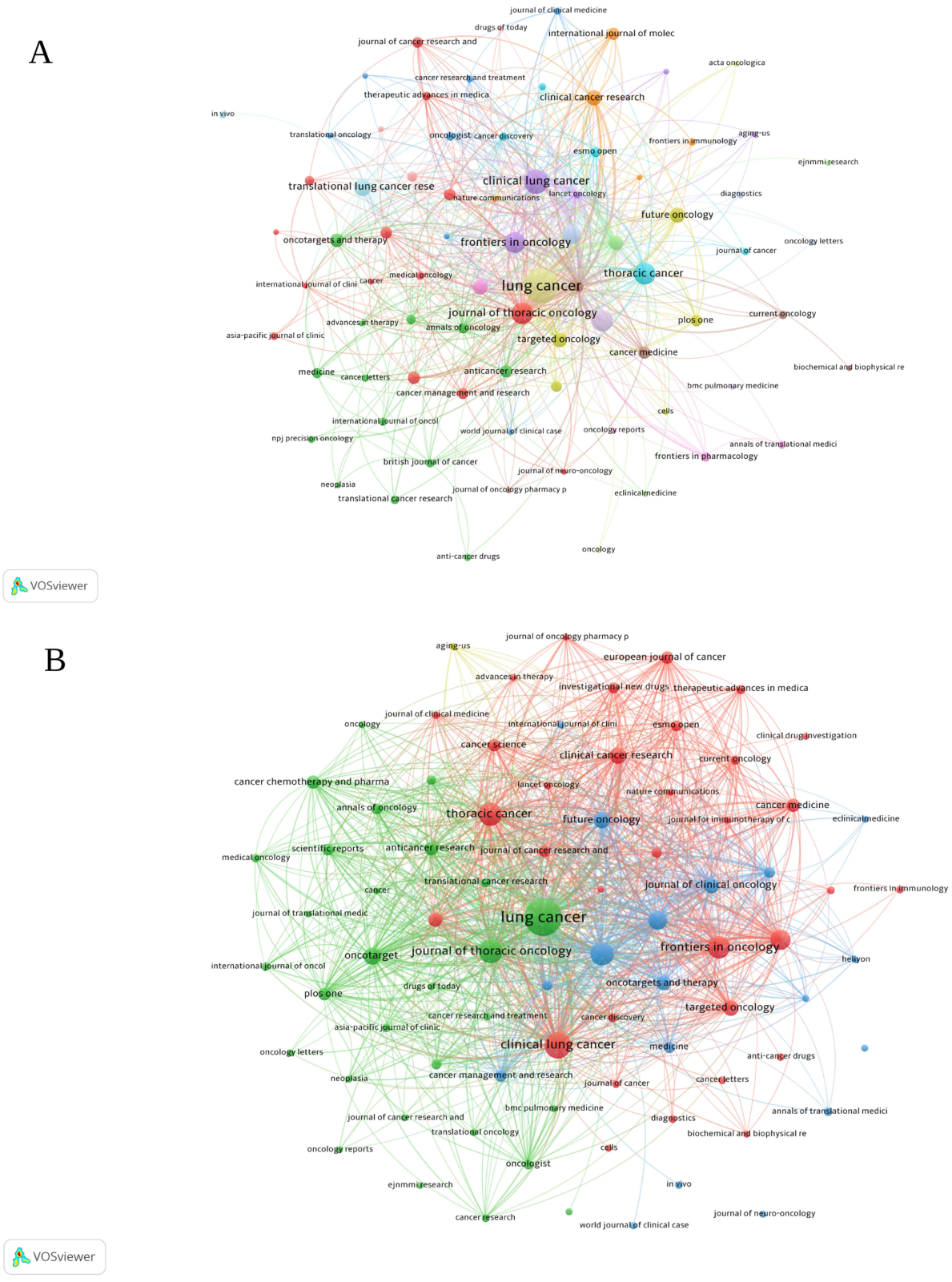


**Figure 6** (**A**) Journal co-occurrence network diagram. (**B**) Journal bibliography coupling network diagram.

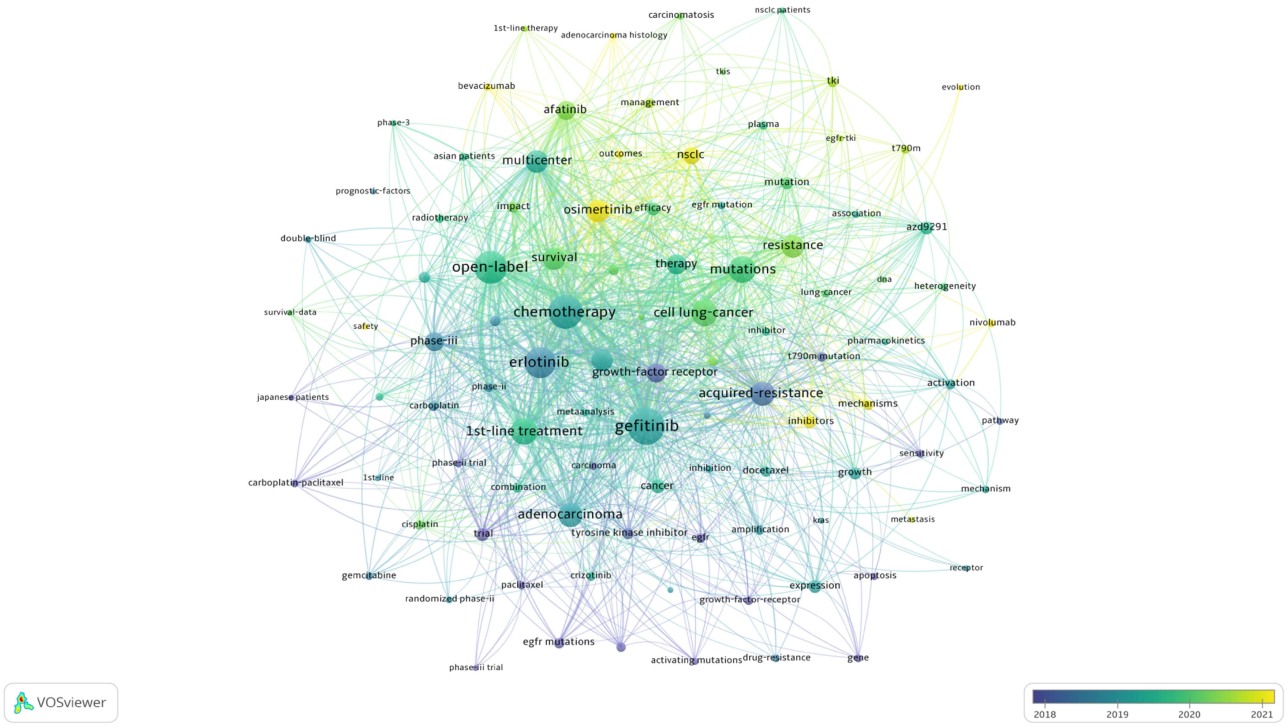


**Figure 7** Visual analysis of keyword co-occurrence network analysis.

## Top 20 Keywords with the Strongest Citation Bursts

| Keywords | Year | Strength | Begin | End | 2006 - 2024 |
|---|---|---|---|---|---|
| growth factor receptor | 2007 | 9.73 | **2007** | 2016 | |
| gene mutations | 2009 | 7.73 | **2009** | 2017 | |
| activating mutations | 2010 | 4.66 | **2010** | 2016 | |
| phase iii | 2011 | 3.5 | **2011** | 2015 | |
| epidermal growth factor receptor | 2006 | 3.58 | **2012** | 2014 | |
| tyrosine kinase inhibitor | 2009 | 4.47 | **2013** | 2014 | |
| egfr mutations | 2013 | 4.02 | **2013** | 2019 | |
| adenocarcinoma | 2013 | 4.54 | **2014** | 2017 | |
| trial | 2008 | 7.5 | **2015** | 2018 | |
| phase ii trial | 2015 | 5.34 | **2015** | 2016 | |
| carboplatin paclitaxel | 2015 | 4.15 | **2015** | 2016 | |
| amplification | 2016 | 4.99 | **2016** | 2017 | |
| azd9291 | 2017 | 5.21 | **2017** | 2018 | |
| radiation therapy | 2018 | 5.81 | **2018** | 2019 | |
| mechanism | 2018 | 3.87 | **2018** | 2019 | |
| liquid biopsy | 2020 | 5.15 | **2020** | 2022 | |
| mechanisms | 2021 | 4.6 | **2021** | 2024 | |
| osimertinib | 2019 | 13.73 | **2022** | 2024 | |
| cisplatin | 2015 | 3.91 | **2022** | 2024 | |
| adjuvant therapy | 2022 | 3.66 | **2022** | 2024 | |

**Figure 8** Top 20 keywords with the strongest citation bursts. The bold formatting "Begin" column indicates the year when the keyword was first proposed, representing the beginning of the research in the relevant direction.


https://doi.org/10.2147/DDDT.S510031

gefitinib and erlotinib, which specifically target these receptors. Peters et al compares the pharmacokinetics of different EGFR TKIs and their potential drug–drug interactions, providing insights into the clinical application of these treatments in NSCLC.[32] The subsequent citation burst for "gene mutations" (2009–2017) marks the increasing emphasis on the genetic underpinnings of NSCLC, particularly the identification of EGFR mutations that predict responsiveness to TKIs. Singh et al highlights the clinical efficacy of EGFR TKIs in treating NSCLC with specific gene mutations such as Exon 19 deletions and L858R mutations in exon 21. It also discusses resistance mechanisms, particularly the T790M mutation, and the development of next-generation inhibitors that selectively target these mutations.[33] The sustained interest in this keyword underscores the pivotal role of gene mutations in not only identifying suitable candidates for TKI therapy but also in understanding mechanisms of resistance, which has become a major focus in later years.

From 2011 to 2015, the keyword "phase III" showed a notable citation burst. This reflects the culmination of research efforts into large-scale clinical trials designed to evaluate the efficacy and safety of various TKIs. This Phase III study conducted in China evaluated the combination of apatinib, a VEGFR2 TKI, with gefitinib as a first-line therapy for advanced EGFR-mutant NSCLC. The study showed a significant improvement in progression-free survival for the combination therapy compared to gefitinib alone.[34] A meta-analysis compares the efficacy of first-line tyrosine kinase inhibitor therapy followed by chemotherapy with the reverse sequence in patients with EGFR-mutated NSCLC, using data from multiple Phase III trials. The results suggest no significant difference in overall survival between the two sequences.[35] The attention given to phase III trials during this time highlights the critical stage of translating molecular insights and early clinical findings into approved therapeutic options for patients with EGFR-mutated NSCLC.

More recently, the bursts for "liquid biopsy" (2020–2022) and "mechanisms" (2021–2024) reflect the field's shift toward non-invasive diagnostic techniques and a deeper exploration of the underlying mechanisms driving cancer progression and resistance to therapy. A retrospective study examined the role of liquid biopsy in detecting resistance mechanisms in NSCLC patients who had failed EGFR-TKI therapy. The findings suggest that liquid biopsy is a useful tool for guiding subsequent treatment decisions.[36] Ruiz et al analyzed the impact of EGFR mutation detection through liquid biopsy on overall survival in NSCLC patients. The results indicated that patients with positive liquid biopsies had significantly lower survival rates, underscoring the importance of early detection and continuous monitoring.[37] Finally, the ongoing citation bursts for keywords such as "cisplatin", and "adjuvant therapy" (2022–2024) highlight current research interests in optimizing and expanding treatment options for EGFR-mutated NSCLC. A Phase 3 study compared gefitinib with vinorelbine plus cisplatin as adjuvant treatments for resected stage II–IIIA EGFR-mutant NSCLC. Gefitinib significantly prolonged disease-free survival compared to the cisplatin-based regimen.[38] The focus on adjuvant therapy suggests an increasing interest in preventing cancer recurrence following primary treatment, which is critical for improving long-term patient outcomes.

Compared to a related bibliometric study published in 2024,[39] which broadly examined TKI research, our study provides a more focused analysis specifically on EGFR-mutated NSCLC. This targeted approach allows us to explore niche trends, such as the emerging role of osimertinib in overcoming T790M resistance mutations, and their implications for clinical practice. Unlike the previous study, which analyzed TKIs as a whole, we examine the mutation-specific impact of TKIs, including Exon 19 deletions, L858R, T790M, and C797S resistance mutations. Additionally, we offer a deeper analysis of institutional and author contributions, highlighting global collaborations and research productivity trends that were not extensively covered in the prior study. Furthermore, our findings reveal a clear shift from first- and second-generation TKIs to third-generation agents like osimertinib, alongside a growing emphasis on overcoming resistance mechanisms—a trend not fully explored in earlier bibliometric analyses. By analyzing keyword co-occurrence trends, we also identify the rising influence of real-world evidence and open-label study designs in TKI research, an aspect that received limited attention in the previous study.

## Strengths and Limitations

The study presents several notable strengths. First, the comprehensive bibliometric analysis provides a detailed overview of research trends and key contributors in the field of TKIs and EGFR-mutated NSCLC, effectively mapping the landscape of this research area. Second, the use of multiple bibliometric tools facilitates robust visualizations of collaborations, keyword co-occurrences, and emerging trends, thereby ensuring a well-rounded understanding of the data.

However, this study also encounters several limitations that warrant acknowledgment. First, the selection of publications was limited to English-language articles, which may introduce selection bias and exclude significant contributions from non-English-speaking regions. This is particularly relevant for countries such as China and Japan, where substantial research on TKIs for EGFR-mutated NSCLC has been conducted. Second, the analysis relied solely on the WoSCC database, which, while comprehensive, may exclude relevant studies indexed in other databases such as Scopus and PubMed. This reliance on a single database may limit the generalizability of the findings and should be factored into the interpretation of results. Third, the timeline of the analysis (2006–2024) introduces potential biases, as recent publications may not yet have accrued sufficient citations to fully reflect their impact. Fourth, while bibliometric tools such as VOSviewer, CiteSpace, and R-bibliometrix are widely used for such analyses, their reliability depends on the parameters and thresholds selected. For example, the keyword node threshold (set at 5 in this study) may influence the sensitivity and specificity of trend detection. Future studies could benefit from validating their findings using alternative tools and methodologies. Lastly, the study's focus on bibliometric metrics such as the H-index, Impact Factor, and citation counts, while useful for assessing influence, does not capture qualitative dimensions of research impact, such as clinical relevance or translational potential. Future work could complement these findings with qualitative analyses to better understand the practical implications of TKI research for clinical practice.

## Conclusion

This bibliometric analysis offers valuable insights into the research landscape of TKIs for EGFR-mutated NSCLC, highlighting key contributors, influential publications, and emerging research trends. The findings underscore the critical role of targeted therapies in advancing treatment options for NSCLC, with a particular emphasis on the significance of TKIs like gefitinib and osimertinib. These insights are essential for guiding future research directions and informing clinical practices in the management of EGFR-mutated NSCLC.

## Data Sharing Statement

All data generated or analysed during this study are included in this published article and its Supplementary Information files.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors declare that they have no competing interests.

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